UNIVERSITY
OF TASMANIA

OCCURRENCE, PRESENTATION, COSTS AND THREE-MONTH OUTCOMES OF STROKE IN VIET NAM

by

Pham Lan Tran MD, MSc, MPH

Submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy (Medical Research)

Menzies Institute for Medical Research
University of Tasmania

July 2015

Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

Signed: 

Date: 08/07/2015

Statements of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Signed: 

Date: 08/07/2015

Statements of authority of access and regarding published work

This thesis may be made available for loan. Copying of any part of this thesis is prohibited for two years from the date this statement was signed; after that time limited copying and communication is permitted in accordance with the Copyright Act 1968.

The publishers of the papers comprising Chapter 3,4,5,6 and 7 hold the copyright for that content, and the access to the material should be sought from the respective journals.

Signed: 

Date: 08/07/2015

Statement of authorship

This thesis includes manuscripts for which Pham Lan Tran (PLT) was not the sole author. PLT was the lead in this research. She participated in study design (the cohort of patients with first-ever stroke with follow-up to three months), conducted data collection (the surveillance of patients with stroke admitted to 115 People's Hospital and the cohort study), analysed data, and prepared and completed revisions to each of the manuscripts. However, she was assisted by the co-authors whose contributions are detailed below.

1. The paper reported in Chapter 3:
Pham LT, Blizzard CL, Gall S, Thrift AG, Luong NK, Truong LVN, Tran TH, Tran QB, Ha TS, Nguyen TKL, Nguyen HT, Phung NH, Tran HM, Magnussen GC, Otahal P, Scott-Mills N, Velandai S. Hospital-based surveillance of stroke over 12 months at a tertiary teaching hospital in Ho Chi Minh City, Viet Nam. Manuscript submitted for consideration of publication in International Journal of Stroke.

The contribution of each author:

PLT participated in data collection, data management, and data cleaning and prepared the initial draft of the manuscript. With CLB, she undertook all of the analyses, interpreted the results and completed revisions to the manuscript.

CLB with PLT undertook all of the analyses and interpreted of the data and revised the manuscript.

SG, AGT, LNK and TLVN assisted with the design and conduct of the study, and with interpretation of the data, and revised the manuscript.

TTH, TQB, HTS, NTKL, NHT, PNH, THM, CGM, PTO and NSM assisted with interpretation of the data and revised the manuscript.

VS was responsible for obtaining approvals and for the design and conduct of the study, assisted with interpretation of the data, and revised the manuscript.

2. The paper reported in Chapter 4
Pham LT, Blizzard CL, Velandai S, Thrift AG, Nguyen TKL, Nguyen HT, Gall S. Case-fatality and functional status three months after first-ever stroke in Viet Nam. Manuscript prepared for a submission for consideration of publication in the European Journal of Neurology.

The contribution of each author:

PLT participated in data collection, data management, and data cleaning and prepared the initial draft of the manuscript. With CLB, she undertook all the analyses and, interpretation of the data, and completed revisions to the manuscript.

CLB assisted with the design and conduct of the study and, with PLT, undertook all of the analyses and interpretation of the data, and revised the manuscript.

VS assisted with the design and conduct of the study and with interpretation of the data, and revised the manuscript.

AGT, NHT and NTKL assisted with interpretation of the data and revised the manuscript.

SG assisted with design and conduct of the study and with analyses and interpretation of the data, and revised the manuscript.

3. The paper reported in Chapter 5
Pham LT, Blizzard CL, Velandai S, Palmer JA, Thrift AG, Cadilhac D, Nguyen TKL, Nguyen HT, Gall S. Cost of first-ever stroke in Viet Nam. Manuscript prepared for a submission for consideration of publication in the journal (Value in Health).

The contribution of each author:

PLT participated in data collection, data management, and data cleaning and prepared the initial draft of the manuscript. With CLB, she undertook all of the analyses and, interpretation of the data, and completed revisions to the manuscript to the manuscript.

CLB assisted with the design and conduct of the study and, with PLT, undertook all of the analyses and interpretation of the data, and revised the manuscript.

VS assisted with the design and conduct of the study and with interpretation of the data, and revised the manuscript.

AGT, PJA, DC, NHT and NTKL assisted with interpretation of the data and revised the manuscript.

SG assisted with design and conduct of the study and with analyses and interpretation of the data, and revised the manuscript.

4. The paper reported in Chapter 6
Pham LT, Blizzard CL, Velandai S, Vo TXH, Nguyen TKL, Nguyen HT, Gall S. Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Viet Nam. This manuscript is accepted for publication in the International of Quality of Life Research journal [1].

The contribution of each author:

PLT participated in data collection, data management, and data cleaning and prepared the initial draft of the manuscript. With CLB, she undertook all of the analyses and interpretation of the data, and completed revisions to the manuscript.

CLB assisted with the design and conduct of the study and, with PLT, undertook all of the analyses and interpretation of the data, and revised the manuscript.

VS assisted with the design and conduct of the study and with interpretation of the data, and revised the manuscript.

VTXH, NHT and NTKL assisted with interpretation of the data and revised the manuscript.

SG assisted with design and conduct of the study and with analyses and interpretation of the data, and revised the manuscript.

5. The paper reported in Chapter 7
Pham LT, Blizzard CL, Velandai S, Thrift GA, Vo TXH, Nguyen TKL, Nguyen HT, Gall S. Health-related quality of life among survivors three months after stroke. Manuscript prepared for a submission for consideration of publication in the journal (Stroke).

The contribution of each author:

PLT participated in data collection, data management, and data cleaning and prepared the initial draft of the manuscript. With CLB, she undertook all of the analyses and interpretation of the data, and completed revisions to the manuscript.

CLB assisted with the design and conduct of the study and, with PLT, undertook all of the analyses and interpretation of the data, and revised the manuscript.

VS assisted with the design and conduct of the study and with interpretation of the data and revised the manuscript.

AGT, VTXH, NHT and NTKL assisted with interpretation of the data, and revised the manuscript.

SG assisted with design and conduct of the study and with analyses and interpretation of the data, and revised the manuscript.

Signed by primary supervisor, Associate Professor Leigh Blizzard

Date: 08/07/2015

Abstract

Background

Stroke is the third most common cause of death in the world and is projected to be the second leading cause by the year 2020. Although rates of stroke mortality have decreased in high income countries (HICs) in recent decades, the burden of stroke may be increasing in low and middle income countries (LMICs) but information is scarce. To address this critical lack of data for Viet Nam, five studies of stroke occurrence, costs of treatment and short-term outcomes were conducted.

Methods

The first study involved surveillance of 5,017 admissions of stroke patients over 12 months at a tertiary public teaching hospital in Ho Chi Minh City. To obtain information on outcomes at three months, 450 consecutive patients with first-ever stroke were followed-up. The remaining four studies of this thesis present findings from this follow-up study.

Results

Principal surveillance findings were that the median age of patients was 65.0 years, ischaemic stroke was the dominant type, the majority of admissions were for first-ever events, and the signs and symptoms of stroke were similar in Viet Nam as elsewhere. Around one-half of patients had scores on the modified Rankin Scale (mRS) corresponding to most severe disability (mRS=4/5). The estimated incidence of hospital-admitted stroke was 105.6 per 100,000 person-years, and the confirmed case-fatality at 28 days was 12.2%.

Case-fatality and functional outcomes at 3 months after stroke were assessed in the second study. With minimal loss to follow-up, case-fatality at 3 months was 10.4% and one-third of survivors had most severe disability (mRS=4/5). Over three months, one-half of patients had improved functional status and one-quarter had worsened, with male patients having greater improvement.

In the third study, information for 437 patients in the cohort was used to estimate the costs of stroke treatment. Average total costs per stroke admission were USD 963 comprising USD 560 for direct medical cost, USD 171 for direct non-medical cost, and USD 240 for indirect costs. Health insurance halved out-of-pocket direct medical costs. Severity of stroke, length of stay and household wealth were the major predictors of cost.

The reliability and validity of the Duke Health Profile (DHP) for assessing the Health Related Quality of Life (HRQoL) of stroke patients was examined in the fourth study of 108 patients and 94 caregivers of patients. They completed the DHP questionnaire and a comparison instrument, the EQ-5D. Each was re-administered after 1 week. Intra-class correlations ranged from 0.60 to 0.86 (patient test-retest) and from 0.55 to 0.98 (patient-proxy agreement). Correlations between DHP and EQ-5D dimensions were strongest for similar constructs (r=0.53–0.66).

The HRQoL of 373 stroke survivors at 3 months was assessed in the fifth study. Their average DHP overall score (58.7) and EQ-5D utility score (0.67) were lower than those from comparable general population samples. Female sex, increasing age, lower SES, severe stroke at admission time and poor functional status at 3 months were predictors of poorer HRQoL.

Conclusions and implications

Young age at stroke onset relative to patients in HICs, and the high proportion with moderate-to-severe disability, confers a high burden of stroke in Viet Nam. The similar clinical presentation suggests that campaigns used in HICs to raise awareness of early signs and symptoms could be adopted in Viet Nam. The comparable factors associated with stroke occurrence and with functional outcomes prompt application of strategies for prevention and management of stroke that are effective in HICs. Despite relatively short average length of stay, the total costs of treatment amounted to 2 and 3 times the median monthly income of insured and non-insured patients, respectively. Broader health insurance coverage of the Vietnamese population would help to bridge the gap. The overload of patients in the stroke unit at this hospital signals the need for more stroke units to be established in other hospitals in HCMC and surrounds. Measurements of HRQoL with the DHP, which has moderate reliability and validity for use with stroke patients in Viet Nam, demonstrated that stroke reduces the reported psychological well-being of survivors, and particularly that of female patients.

Acknowledgement

My PhD was a long and ambitious journey. At the beginning, in 2011, I could not imagine how difficult and challenging it could be. Had I not been supported by my supervisors, advisors, friends and families, I would not be able to reach the end of the journey.

First of all, my greatest gratitude goes to my primary supervisor, Associate Professor Leigh Blizzard, for his patience and endless support throughout my PhD research. Without his help, I would still be a novice in the field of complex data analysis. I truly thank him for his valuable time spent with me during my PhD, especially the period of field study in Viet Nam. I will never forget the moment we travelled by a small fishing boat to visit a stroke survivor at her home located on a small island near Ho Chi Minh City. I realised that our hearts were touched when we saw the tragic consequences of stroke on that patient and her family. Such repercussions of stroke on patients and their families have motivated and encouraged me to work harder in my PhD research to produce valuable information on outcomes of stroke in Viet Nam.

I would also like to thank my co-supervisors, Associate Professor Velandai Srikanth and Dr Seana Gall. It has been more than 5 years since the time I first met the two of you at 115 People's Hospital in Ho Chi Minh City, Viet Nam. When I handed my "preliminary" protocol to Associate Professor Velandai Srikanth, I had a dream to conduct a further investigation of stroke in Viet Nam. And now that dream has become reality with my ideas for the study approved and utilised in my PhD. Thank you for giving me a chance to work with you in your 12-month stroke surveillance project in Ho Chi Minh City, Viet Nam. Thank you for your trust, help and support that have encouraged me to be persistent on the path of stroke research in Viet Nam.

Special thanks to my dear advisors, Professor Amanda Thrift and Associate Professor Dominique Cadilhac from Stroke and Ageing Research Centre, School of Clinical Sciences at Monash University and Professor Andrew Palmer from Health Economic Unit at Menzies Institute for Medical Research, for their continuous advice during my PhD research from the protocol through to final papers. I have gained a significant amount of knowledge of health economics and stroke epidemiology from them.

I would like to express my appreciation to all of my dear research assistants at Pham Ngoc Thach University of Medicine and 115 People's Hospital in Ho Chi Minh City, Viet Nam. Thank you for your help and patience in following up the study participants and collecting excellent quality data from patients with stroke in our cohort.

I am greatly appreciative of the financial support provided by Atlantic Philantropies Inc. and the Menzies Institute for Medical Research, and for the Tasmania International Postgraduate Scholarship awarded by the University of Tasmania. I truly treasure the great work environment at Menzies Institute for Medical Research.

Special thanks to my wonderful Vietnamese friends and families in Hobart, Melbourne and Canberra: Uncle Mien Le, Phuong Nguyen, Tien Ho, Khanh Nguyen, Duc Nguyen, Thuy Au,

Van Nguyen and Hoang Phan. You have been given me a fabulous “adopted” family in Australia while I was far away from my family in Viet Nam.

I am deeply grateful to my parents, my mother-in-law and relatives in Viet Nam. As always, their continuous love, support and expectations have nourished me.

Last but not least, I am deeply indebted to my husband, Thong Hua, for his love, sacrifices and encouragement during my study. It was not an easy decision when Thong decided to give up his career as a cardiologist in Viet Nam to come to Australia to support me during the last 3 years. My doting son, Minh Hua, has been my motivation to overcome all challenges on my journey.

Pham Lan Tran.

June 2015

Table of contents

List of tables

List of figures

List of abbreviations

CI	:	Confidence interval
COI	:	Cost of illness
CT scan	:	Computerised tomography scan
DHP	:	Duke Health Profile
EQ5D	:	European Quality of Life
EQ-VAS	:	European Quality of life- visual analogue scale
HCMC	:	Ho Chi Minh City
HICs	:	High income countries
HRQoL	:	Health Related Quality of Life
ICF	:	International Classification of Functioning Disability and Health
ICH	:	Intracerebral haemorrhage
ICU	:	Intensive Care Unit
IS	:	Ischaemic stroke
LMICs	:	Low and middle income countries
LOS	:	Length of stay
MoH	:	Ministry of Health
MRI	:	Magnetic resonance imaging
mRS	:	Modified Rankin Scale
NICE	:	National Institute for Health and Care Excellence
NIHSS	:	National Institutes of Health Stroke Scale
OCSP	:	The Oxfordshire Community Stroke Project Classification
rFVIIa	:	Activated recombinant factor VII
r-tPA	:	Recombinant tissue plasminogen activator
SAH	:	Subarachnoid haemorrhage
SF-36	:	Short Form 36
TIA	:	Transient ischemic attack
WHO	:	World Health Organization
WHO-QoL	:	World Health Organization Quality of Life

Conference presentations using the work described in this thesis

Tran Pham, Leigh Blizzard, Seana Gall, Velandai Srikanth. Health-related quality of life assessment after stroke: examination of the validity of the Duke Health Profile for use with stroke patients in Vietnam. Tasmania Health Science HDR Student Conference, University of Tasmania, Hobart, July 2013. Oral presentation.

Tran Pham, C Leigh Blizzard, Luong Ngoc Khue, Ly Ngoc Kinh, Seana Gall, Amanda Thrift, Truong Le Van Ngoc, Tran Thanh Huong, Tran Quoc Bao, Ha Thai Son, Nguyen Thi Kim Lien, Nguyen Huy Thang, Phung Ngoc Hai, Tran Hoang Mai, Petr Otaha1, Nicholas Scott-Mills, Velandai Srikanth. Incidence of stroke in Ho Chi Minh City, Viet Nam. Sharing Excellence in Research Conference, University of Tasmania, Hobart, September 2013. Poster presentation.

Tran Pham, C Leigh Blizzard, Luong Ngoc Khue, Ly Ngoc Kinh, Seana Gall, Amanda Thrift, Truong Le Van Ngoc, Tran Thanh Huong, Tran Quoc Bao, Ha Thai Son, Nguyen Thi Kim Lien, Nguyen Huy Thang, Phung Ngoc Hai, Tran Hoang Mai, Petr Otaha1, Nicholas Scott-Mills, Velandai Srikanth. Incidence of stroke in Ho Chi Minh City, Viet Nam. Australasian Epidemiological Association (AEA) Annual Meeting, Brisbane 2013. Poster presentation.

Tran Lan Pham, C Leigh Blizzard, Velandai Srikanth, Nguyen Thi Kim Lien, Nguyen Huy Thang, Andrew Palmer, Dominique Cadilhac, Seana Gall. Direct in-hospital costs for stroke patients admitted to a stroke unit in Ho Chi Minh City, Viet Nam. European Stroke Conference, Nice, France May 2014. E-poster presentation.

Tran Lan Pham, C Leigh Blizzard, Velandai Srikanth, Nguyen Thi Kim Lien, Nguyen Huy Thang, Seana Gall. Outcomes at 3 month after first-ever stroke in Ho Chi Minh City, Viet Nam. European Stroke Conference, Nice, France May 2014. E-poster presentation.

Tran Lan Pham, C Leigh Blizzard, Velandai Srikanth, Nguyen Thi Kim Lien, Nguyen Huy Thang, Seana Gall. Mortality, disability and health-related quality of life at 3 month after first-ever stroke in Ho Chi Minh City, Viet Nam. Stroke Society Australasian (SSA) Annual Meeting, Hamilton, August 2014. Oral presentation.

Tran Lan Pham, C Leigh Blizzard, Velandai Srikanth, Dominique Cadilhac, Nguyen Thi Kim Lien, Nguyen Huy Thang, Andrew Palmer, Seana Gall. Treatment costs for stroke patients admitted to a stroke unit in HoChiMinh City, Vietnam. Stroke Society Australasian (SSA) Annual Meeting, Hamilton, August 2014. Poster presentation.

Tran Lan Pham, C Leigh Blizzard, Velandai Srikanth, Dominique Cadilhac, Nguyen Thi Kim Lien, Nguyen Huy Thang, Andrew Palmer, Seana Gall. Treatment costs for stroke patients admitted to a stroke unit in Ho Chi Minh City, Vietnam. Sharing Excellence in Research Conference, University of Tasmania, Hobart 2014. Poster presentation.

Tran Lan Pham, C Leigh Blizzard, Velandai Srikanth, Dominique Cadilhac, Nguyen Thi Kim Lien, Nguyen HuyThang, Andrew Palmer, Seana Gall. Hospital costs for stroke patients admitted to a stroke unit in Ho Chi Minh City, Viet Nam. Australasian Epidemiological Association (AEA) Annual Meeting, Auckland 2014. Poster presentation.

Tran L Pham, C Leigh Blizzard, Velandai Srikanth, Andrew J. Palmer, Amanda G Thrift, Dominique Cadilhac, Nguyen Thi Kim Lien, Nguyen Huy Thang, Seana L Gall. Non-medical costs and indirect costs of stroke in Viet Nam. Stroke Society Australasian (SSA) Annual Meeting, Melbourne, September 2015. Poster presentation (confirmed)

Tran L Pham, C Leigh Blizzard, Velandai Srikanth, Amanda G Thrift, Vo T Xuan Hanh, Nguyen Thi Kim Lien, Nguyen Huy Thang Seana L Gall1. Predictors of health-related quality of life of stroke survivors in Viet Nam. Stroke Society Australasian (SSA) Annual Meeting, Melbourne, September 2015. Oral presentation (confirmed)

Award received from the work describe in this thesis

UTAS Graduate Research Travel and Conference grant for attending the European Stroke Conference 2014 in Nice, France.

Publication directly arising from the work described in this thesis

Chapter 6:

Tran, P. L., Leigh Blizzard, C., Srikanth, V., Hanh, V. T., Lien, N. T., Thang, N. H., et al. (2015). Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Vietnam. *Qual Life Res* (Article in press).

Other publications

Gall, S. L., Tran, P. L., Martin, K., Blizzard, L., & Srikanth, V. (2012). Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. *Stroke*, 43(7), 1982-7.

Chapter 1: Introduction

1.1. Preface

Stroke was ranked as the second most common cause of death and the third most common cause of disability-adjusted life-years worldwide in 2010 [2]. This thesis explores the epidemiology of stroke in a hospital-based setting in Ho Chi Minh City, Viet Nam. It reports findings from a series of studies of the burden of stroke in Viet Nam. Those studies include 12 months surveillance of stroke at a major teaching hospital in Ho Chi Minh City, an investigation of costs of treatment of stroke in hospital, and a three-month follow-up of survivors to elicit information on outcomes and health-related quality of life (HRQoL) at that time. This introductory chapter provides background information on key issues including the clinical manifestation of stroke, the burden of stroke in lower and middle income countries (LMICs) and a description of the study setting including the healthcare system in Viet Nam.

1.2. Clinical manifestation of stroke

1.2.1. Definition of stroke

Stroke has been defined by the World Health Organization (WHO) as "rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" [3]. This definition excludes transient ischemic attack (TIA, defined as focal neurological symptoms that last less than 24 hours), subdural haemorrhage, epidural haemorrhage, poisoning and symptoms caused by trauma [4]. First-ever stroke is defined as a stroke occurring for the first time during a patient's lifetime [5].

The American Heart Association has recently developed an updated definition of stroke and transient ischaemic attack (TIA). The major difference in the updated definition is the recognition of the role of imaging in diagnosis, removing the emphasis on time in the earlier WHO definition. The updated definition classifies central nervous system infarction as "brain, spinal cord, or retinal cell death attributable to ischemia, based on either pathological, imaging, or other objective evidence of focal ischemic injury in a defined vascular distribution, or clinical evidence of focal ischemic injury based on symptoms persisting $\geq$ 24 hours or until death, and other aetiologies excluded" [5]. Ischaemic stroke (IS) has been defined as "an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction". The definition of stroke caused by intracerebral haemorrhage (ICH) is "rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma". A stroke caused by subarachnoid haemorrhage (SAH) has been defined as "rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma". Those who suffer transient sudden focal neurological symptoms < 24 hours of presumed vascular origin, but without demonstrable infarction or haemorrhage on brain imaging, are classified as having a transient ischaemic attack (TIA) [5].

1.2.2. Pathological types of stroke

Worldwide, IS account for 80-85% of stroke. Haemorrhagic stroke, including ICH and SAH, account for 15-20% of strokes [6].

These major stroke types are often further classified according either to the region of the brain they affect or their aetiology. The Oxfordshire Community Stroke Project Classification (OCSP) [7] is an old clinical classification, categorising strokes into four regional subtypes including total anterior, partial anterior, lacunar and posterior circulation infarcts. In the absence of advanced brain imaging techniques, this classification was based on the clinical presentation alone and therefore the accuracy of this system has some limitation. [8,9]. The most commonly-used classification system for the aetiology of stroke is that used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [10] that use all available clinical and diagnostic test information to categorise IS into 5 subtypes: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined aetiology, and 5) stroke of undetermined aetiology. Treatment guidelines and prognosis differ depending on the type of stroke.

Table 1.1 shows the distribution of types of stroke in a number of LMICs. IS is usually the dominant type of stroke, ranging from 64.4% in Nigeria [11] to 80.2% in Mumbai, India [12]. The incidence of haemorrhagic stroke has increased in LMICs during the 20 years from 1990 to 2010 [13]. It is notable that ICH has been found to be more prevalent in India, Nigeria and China [11,14,15].

Table 1.1: Distribution of types of stroke in LMICs.

Location	Source	IS	ICH	SAH
High income countries	[16]	82.0%	11.0%	3.0%
Low and middle income countries	[16]	67.0%	22.0%	7.0%
Mumbai, India	[12]	80.2%	17.7%	N.A.
Kolkata, India	[17]	68.0%	32.0%	N.A.
Izmir, Turkey	[18]	77.0%	19.0%	4.0%
Chennai, India	[19]	77.0%	17.0%	3.0%
Nigeria	[11]	64.4%	31.7%	3.0%
Fortaleza, Brazil	[20]	72.9%	15.2%	6.0%
Matao, Brazil	[21]	85.2%	13.6%	1.2%

In a recent review, the pooled proportions of IS and ICH in high income countries (HICs) were found to be 82% and 11% respectively during the period 2000-08 [18]. During the same period, the pooled proportional frequency of IS in LMICs (67%) was much lower than that in HICs (82%) and the proportional frequency of haemorrhagic stroke in LMICs was much higher with a doubling of primary ICH (22% in LMICs vs 11% in HICs) and SAH (7% in LMICs vs 3% in HICs) [16]. The increasing relative frequency of haemorrhagic strokes in LMICs may be due to changes in, and the increasing prevalence of, risk factors for stroke in those countries [16,22]. The risk factors are outlined in the next section.

1.2.3. Risk factors for stroke

Non-modifiable risk factors

Non-modifiable risk factors are those that cannot be directly altered by interventions. The major non-modifiable risk factors of stroke are advanced age and male sex. The pattern of increasing incidence of stroke at greater ages becomes particularly apparent after the age of 55 years [2,23-25]. Although this pattern is found in both high income countries (HICs) and LMICs, there is a notable shift in the distribution towards lesser average age of initial stroke onset in LMICs (**Table 1.2**). For example, the mean age of patients with stroke in previous studies conducted in LMICs ranged from 54.5 years in Bangalore [26], India, to 68.0 years in Nigeria [11]. The average age of stroke patients from 9 surveillance sites in 5 different LMICs was found to be 64.2 years by Truelsen et al. [27]. In comparison, the mean age of onset is around 10 years greater in HICs [27]. Possible explanations of why stroke develops at lesser ages on average in LMICs than in HICs are discussed in the following section on modifiable risk factors for stroke.

Table 1.2: Average age at stroke onset from stroke surveillance studies in LMICs.

		Overall	Male	Female
Location	Source	Mean (SD)	Mean (SD)	Mean (SD)
HICs	[2]	74.5 (0.13)		
LMICs	[2]	69.4 (0.17)		
Mumbai, India	[12]	66.0 (13.6)	63.4 (13.5)	68.9 (13.1)
Ibanda,Nigeria	[27]	60.5 (13.1)		
Chennai, India	[19]	61.7 (13.4)		
Bangalore, India	[26]	54.5 (17.0)		
Trivandrum, India	[28]	65.7 (12.1)		
Isfasan, Iran	[27]	68.1 (13.1)		
Maputo, Mozambique	[27]	57.6 (12.6)		
Matao, Brazil	[21]	N.A.	65.1 (11.6)	65.3(12.1)
Moscow 1,Russia	[27]	68.4 (12.2)		
Rural Nigeria	[11]	68.0 (12.0)		
Indonesia	[29]	58.8 (13.3)	57.5 (12.7)	60.4 (13.8)
Sao Paulo, Brazil	[30]	68.0 (14.0)		
Izmir, Turkey	[18]	62.3 (12.0)		
Fortaleza, Brazil	[20]	67.7(14.4)		

The male/female differences in mean age of onset in three LMICs shown in the final two columns of Table 1.2 are consistent with general findings that whilst age-specific rates of stroke are higher among men than women, women survive to greater ages on average and accumulate greater numbers of strokes at advanced ages. In a recent review of stroke in HICs [24], the incidence of stroke was found to be about 25% to 30% higher among men, with a larger male predominance in the populations of Australia, New Zealand and the Americas than in the populations of Europe. The greater life expectancy of women than men, coupled

with the increased risk of stroke at greater ages, means that the absolute number of strokes occurring among women is greater than the number occurring among men.

In Viet Nam, the percentage of the population over 60 years (the ageing index in the context of a developing country) has risen from 18.2% in 1989 to 24.3% in 1999 and 35.5% in 2009, with the expectation of further increases in the future [31]. This demographic transition suggests a rising burden from stroke in coming years.

Whilst beyond the scope of this thesis, there are important questions about differences in treatment of men and women following stroke. For example, some studies show that women more often have severe strokes but conversely are less likely to receive evidence-based care [32-37]. Studies in HICs have investigated social and cultural factors specific to women that may impact on receiving stroke care, such as the fact that women more often live alone than men. Some authors have suggested that women may have greater delays in seeking care due to their neglect of stroke warning signs [32,38]. The extent to which these associations hold true in LMICs, which have different social and cultural structures relating to women and families, is uncertain. What is known is that hospitalisation for stroke is relatively more common for males in LMICs [24]. The male to female ratio of hospital admission was around 1.1 in studies conducted in Indonesia (53.8% of hospitalisations were of males) [29], Brazil (54.7%) [30] and Turkey (55.6%) [18], and as high as 1.9 in Chennai, India (65.9%) [19].

Modifiable risk factors

Modifiable risk factors for stroke are those that may be controlled by lifestyle or pharmacological intervention. The best quality and most up-to-date evidence on modifiable risk factors for stroke has been provided by the INTERSTROKE study, which was a multi-centre case-control study conducted in 22 countries [39]. The major risk factors for stroke were identified as history of hypertension, current smoking, abdominal obesity, poor diet, physical inactivity, diabetes mellitus, excessive alcohol intake, psychosocial stress and depression, cardiac causes, and ratio of lipoproteins B and A1. These were found to be responsible for 90% of strokes [39]. The results of INTERSTROKE largely confirmed findings from earlier case-control and cohort studies of the risk factors for stroke [40-47]. Although there was some variation in the risk factors for IS and ICH, they were generally similar. In this study, high blood pressure and smoking were stronger risks for ICH than for IS. The INTERSTROKE study did not examine the major risk factors for SAH. Other studies have shown that the risk factors for SAH include oral contraceptive use and hormone replacement [48-50], high blood pressure [49], cigarette smoking [49-51] and heavy alcohol consumption [52].

Although INTERSTROKE included data from some LMICs – including Argentina, Brazil, Chile, China, Colombia, Croatia, Ecuador, India, Malaysia, Mozambique, Nigeria, Peru, Philippines, South Africa, Sudan, and Uganda – there is some concern that the findings of the study are not truly generalizable to the entire populations of these countries [53]. This is because participants were recruited from large hospitals, whereas many people suffering stroke would not be treated in such facilities. However, other studies have suggested that the risk factors of stroke in LMICs are relative similar to those in HICs [15,28,54-60]. For example, as in western countries, high blood pressure is considered to be a major modifiable risk factor of stroke throughout the developing world [61] including rural South Africa [62] and South Asia [63].

In recognition of these common risk factors, concerns have been raised regarding a pending "epidemic" [64,65] of stroke within LMICs that have experienced rapid industrialisation in recent decades. This industrialisation has led to improved economic conditions particularly in urban areas, and an accompanying reduction in the burden of infectious, nutritional, and perinatal diseases due to increased availability of clean water, food, shelter and medical care. In consequence, many more people are surviving to the ages at which non-communicable diseases, including stroke, become more common. Increased urbanisation has resulted in reductions in physical activity and significant dietary changes [66]. Diets in the developing world now contain much higher levels of fat, salt and sugar that are associated with increases in blood pressure, serum cholesterol levels and body weight [64-66].

Additionally, the relative strength of a risk factor and the proportion of cases attributable to it each depends on its population prevalence relative to the prevalence of other risk factors. A recent meta-analysis of 22 community-based cohort studies has shown that the importance of risk factors for stroke differs between Western and Asian countries [67] because some risk factors are more prevalent in LMICs than HICs [68]. For example, the prevalence of diabetes is reported to be higher in the populations of some developing regions such as Martinique, West Indies [38], and Latin American [69] than in the populations of developed countries. One study from the Eastern Stroke Coronary Heart Disease Collaborative Research Group [70] found a stronger association between high blood pressure and stroke in Eastern Asia countries than is reported for developed countries [71]. Although tobacco smoking provides a relatively low elevation in risk of stroke occurrence in LMICs [68,72], the burden of stroke related to smoking and cases attributable to it is greater due to the high prevalence of smoking in some of those countries [67,68,72]. In addition, the increasing prevalence of obesity, high blood pressure and excessive alcohol consumption in LMIC populations may contribute to mounting stroke incidence in those countries [72].

There is evidence that some aspects of the lifestyle of Vietnamese people – particularly high intake of fatty and salty foods [66] and high prevalence of tobacco smoking among men – confer elevated risk of stroke. Data from the national survey on risk factors for non-communicable disease conducted during 2009-2010 in Viet Nam showed that 57.7% of men and 1.7% of women aged 25-64 years were current smokers and that 18.5% of men and 10.2% of women had hypertension [73]. The limited data that are available suggest that the prevalence of smoking, excessive alcohol consumption, overweight and obesity, high blood pressure and diabetes have each increased in recent decades. For example, the prevalence of obesity among Vietnamese adults aged 25-64 years is reported to have nearly doubled from 2000 to 2005 (increasing from 3.5% to 6.6%) [66]. If there is to be an "epidemic" of stroke in LMICs, Viet Nam is a potential candidate to be a victim.

1.2.4. Diagnosis

Stroke is diagnosed based on medical history, clinical examination, findings from brain CT scans or MRI, vascular imaging (e.g. extracranial ultrasound and angiography) and cardiovascular examination [74]. Signs and symptoms of stroke include the following: 1) motor impairments (paresis or paralysis of face or other parts of the body, on one or both sides); 2) sensory deficits (touch, pain, warm/cold); 3) speech difficulties or slurred speech; 4) hemianopia (decreased vision, blurred vision); 5) dizziness, gait disturbance, convulsion; 6) headache; and 7) difficulty swallowing. Those who have had a haemorrhagic stroke (ICH) are

more likely to have headache and convulsions, while a relatively greater proportion of patients with IS have speech difficulty and sensory deficits [75,76].

The data relating to the signs and symptoms of stroke are derived largely from studies conducted in HICs, and it is not certain that the same patterns are evident in LMICs. In addition, it is important to understand the presentation of stroke in different settings and different population sub-groups such as men and women, because information about signs and symptoms are used to raise community awareness of stroke and of the need to seek medical attention. Currently there is no information for Viet Nam regarding the major signs and symptoms and, in consequence, no evidence base for determining whether awareness-raising campaigns developed in HICs – such as the Face, Arm, Speech Test (FAST) [77] – can be applied in that country.

1.2.5. Treatment

The treatment of stroke is focused on achieving reperfusion for IS and limiting bleeding for ICH, and managing the downstream effects of the neurological injury resulting from the stroke [78]. In guidelines for acute stroke management by the American Heart Association, it is acknowledged that the first 24 hours of treatment are particularly important including management of airways, blood pressure, temperature, infection, blood glucose, fluid and electrolytes balances and controlling seizures are particularly important [79,80].

Each subtype of stroke requires a different treatment strategy [76]. For IS, intravenous recombinant tissue plasminogen activator (r-tPA) is recommended within first 3 hours to improve outcomes [81-84]. Combined treatment with intravenous and intra-arterial thrombolysis, also known as bridging therapy, has acceptable safety and efficacy for treatment of stroke patients [85]. For ICH, although activated recombinant factor VII (rFVIIa) can limit hematoma expansion, the improvements of outcomes following this treatment has not been proven [86]. If there is severely elevated intracranial pressure, surgery with craniotomy is sometimes required [87]. Anderson et al. [88] showed that patients had better outcomes in terms of limiting hematoma expansion when treated early with intensive blood pressure lowering, but the association of early blood pressure control and hematoma expansion became non-significant after adjustment for initial haematoma volume [88]. Therefore, more evidence is required before it can be accepted that blood pressure lowering therapy improves outcomes following ICH [89]. The recommended treatment of SAH from ruptured aneurysms includes strict control of blood pressure and securing the aneurysm [90]. The aneurysm can be clipped or intravascular coiling can be used, ideally as early as possible [90,91].

In a review of acute treatment and management of stroke in LMICs, Brainin et al. concluded that the quality and quantity of stroke care in those countries varied widely and depended on patient-level factors such as their location, socioeconomic status, education and even cultural beliefs [22,58]. Whether this is the case in Viet Nam is unknown, because there are limited data on clinical care pathways and outcomes following stroke in that country.

1.3. Burden of stroke

The WHO estimated that stroke accounted for 6.7 million deaths worldwide (11.9% of all deaths) in 2012. It has been projected that four out of five stroke victims in 2025 will be

people living in LMICs [27,92]. However, these estimates are based on projections of data from non-representative samples. Therefore, it is essential to obtain epidemiological data on occurrence of stroke in LMICs including estimates of incidence, prevalence and case-fatality. These data are needed to inform decisions about the allocations of resources that are needed to meet the increasing needs of patients with stroke and their families. These data can also be used to plan and evaluate intervention programmes to reduce the burden of stroke and improve outcomes in LMICs [27].

There are many ways to measure the burden of stroke within a population. In this thesis, the author examines the burden of stroke on society, the healthcare system and patients in terms of occurrence of stroke, functional outcomes, economic costs and health-related quality of life (see **Figure 1.1**).

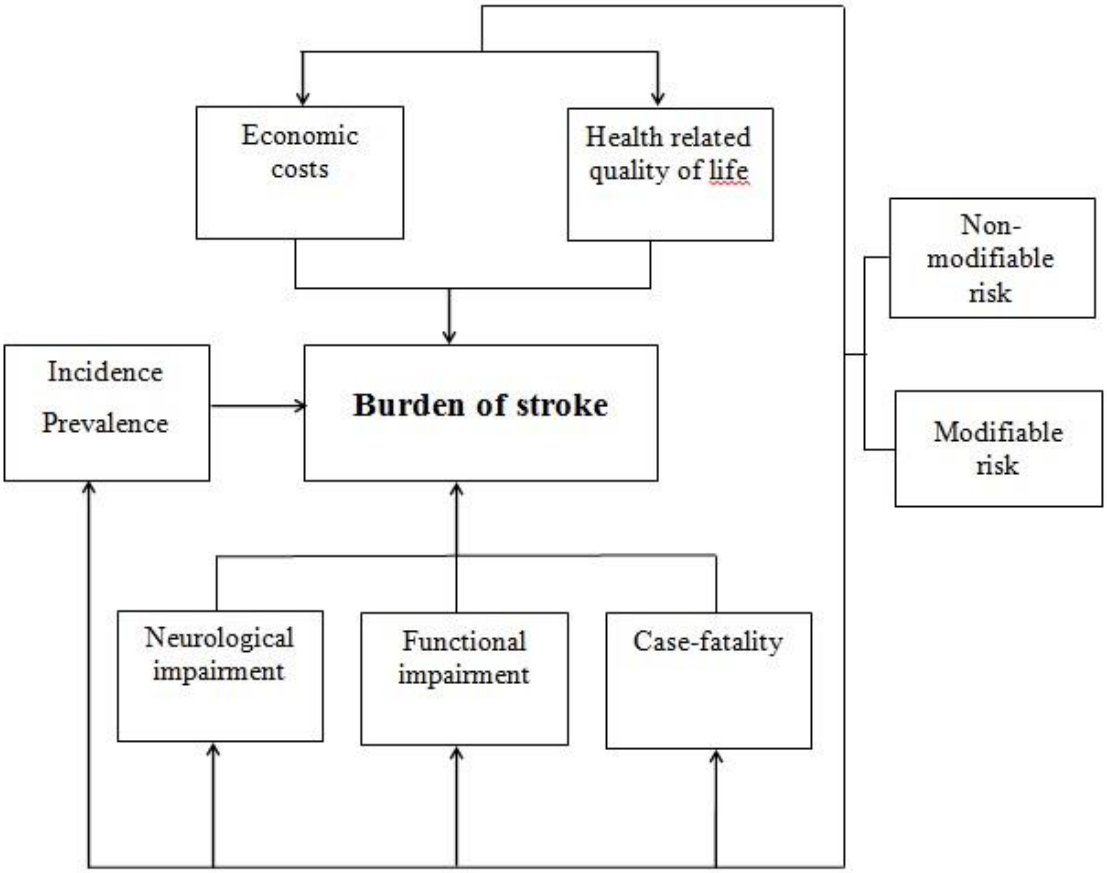


Figure 1.1: Conceptual framework of burden of stroke

1.3.1. Population-based measures of the occurrence of stroke

The three population-based measures of occurrence are incidence, prevalence and mortality. The incidence of stroke is defined as the number of new cases of stroke occurring during a specified period in a population at risk of stroke. New cases of stroke include both first-ever stroke (a first event of stroke for an individual) and recurrent stroke (an event of stroke subsequent to the first event for an individual). The prevalence of stroke is defined as the number of people with stroke (new and old cases) in a population at a particular point in time. It combines measures of incidence and survival. The mortality from stroke is the number of

deaths recorded as being due to stroke during a specified period in a population at risk of stroke. This information can be sourced from routine death registrations if cause of death is determined and recorded. It therefore has the disadvantage of only capturing events that resulted in death, which may only be 17-30% of strokes in HICs and 18-30% in LMICs based on early case-fatality during the period 2000-08 reported in the review by Feigin et al. [16].

Incidence of stroke

Measurement of incidence of stroke

Measuring the incidence of any disease is difficult but the wide ranging severity of strokes and the disparate outcomes following treatment means that capturing all events requires monitoring of many layers of the healthcare system. Acknowledging this, and other issues related to gathering data on stroke, guidelines were developed for conducting the "ideal" stroke incidence study first by Malmgren et al. (1987) [93] and then updated by Sudlow and Warlow (1996) [94] and Coull et al. (2004) [95]. These methods were developed to ensure complete capture of stroke cases in the community irrespective of stroke severity by using multiple overlapping sources of case ascertainment. These could include records of hospital admissions and discharges, general and specialist practitioners, nursing homes, community-based allied health settings and death registries where they exist. To collect all appropriate data, reduce selection bias and improve the accuracy of clinical data, these "'ideal" studies would need to be prospective over at least one year and conducted in a well-defined geographic region with a stable population that provides an accurate denominator for incidence calculations [96].

Such studies have been conducted in various locations across the world (see **Figure 1.2**, which is taken from the review of Feigin et al. [16]). It is evident that most of these studies have been conducted in HICs including Finland, Denmark, France, Sweden, Italy, Norway, Portugal, UK, Russia, Ukraine, USA, Australia and New Zealand [16], with only a small number of studies in LMICs such as India [12] and Brazil [21].

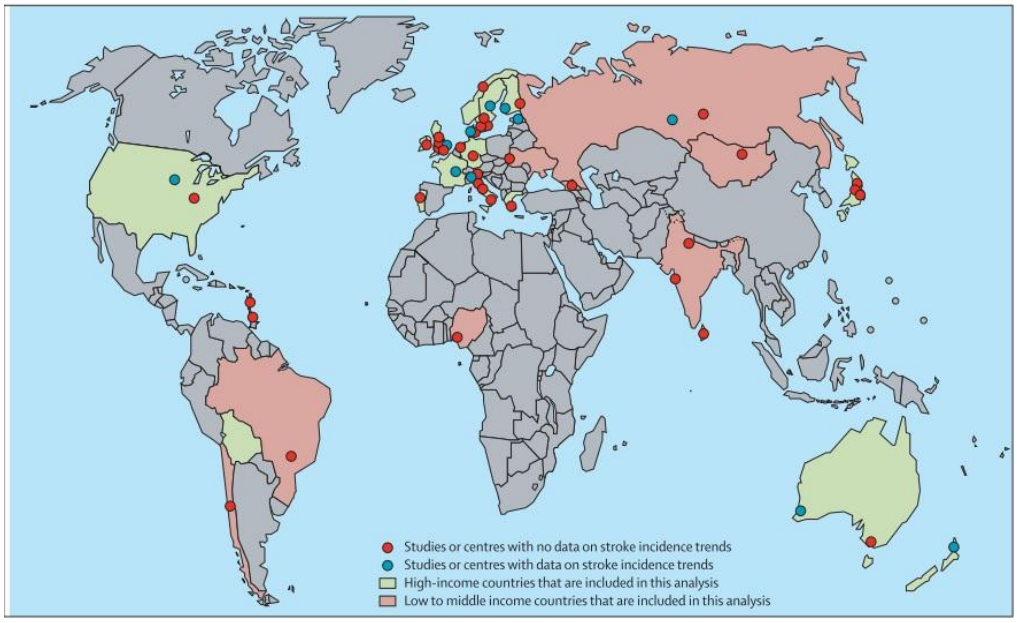


Figure 1.2: World map showing areas of population-based stroke incidence studies.

A major reason for the lack of stroke incidence data for LMICs is the lack of resources with which to conduct these studies. It is not possible, at present, for many LMICs to meet the requirements for an ideal stroke incidence study. Their populations are often fast growing, particularly in urban areas, and routine monitoring of deaths at a population level is not reliable or not available due to the lack of medically-certified cause-of-death data. There is also a lack of funding, infrastructure and suitably trained researchers required to undertake these types of studies. Therefore, the methodology required for an "ideal" incidence study is very difficult to apply in LMICs.

To standardise the process of data collection to make data on stroke comparable between different LMICs and across time, the WHO – in collaboration with the World Stroke Organisation (formerly the International Stroke Society and the World Stroke Federation) – developed a standardised stepwise approach to measuring the burden of stroke. This standardised methodology is termed STEPS-Stroke. It is designed to allow data collection to be tailored to the limited resources that are available in each LMIC [97,98].

The STEPS-Stroke method covers three 'Steps' for finding cases of stroke for a defined population (see **Figure 1.3**). Each Step has a core and expanded dataset with the different levels of data collection increasing in complexity, as detailed below.

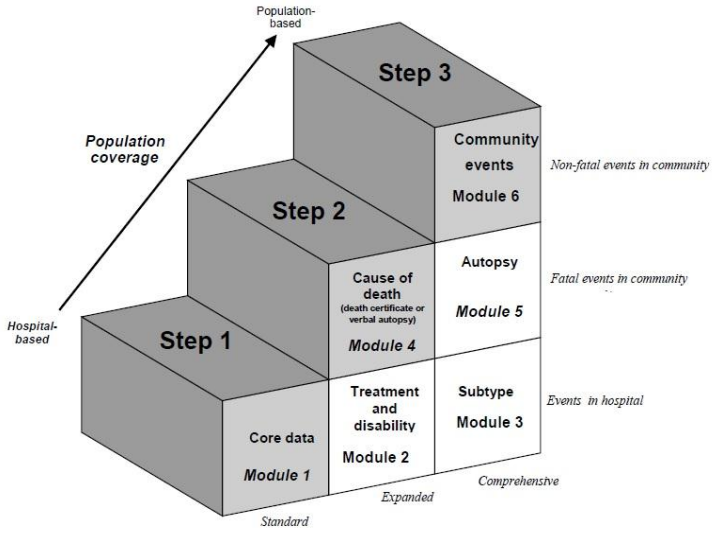


Figure 1.3: The proposed WHO stepwise approach to stroke surveillance.

Step 1 (hospitalised events) focuses on persons who are admitted to a hospital following a stroke defined using the WHO definition. A hospital-based registry is required to collect core data on stroke admissions, severity of stroke and short-term survival. The expanded data requirement of Step 1, if adopted, is for information on exposure of major risk factors before stroke onset to be collected and for assessments of functional status at discharge to be made. A comprehensive implementation of Step 1 is possible if neuroimaging facilities are available at the hospital to validate diagnosis and determine stroke sub-type. If the catchment area of the hospital is well-defined and census data are available on the population of that catchment area, the incidence density of hospital-admitted stroke can be determined. This is an under-estimate of all cases of stroke if very mild cases and very severe cases resulting in rapid death do not present to hospital.

Step 2 (fatal events in community) involves the collection of information on fatal stroke events that have occurred in the same community but out of hospital. If cause-of-death

certification is undertaken in the community, an assessment of its validity must be undertaken prior to the acceptance of information from death certificates. Verbal autopsy techniques are recommended to verify a stroke death. The main outcomes of Step 2 are estimates of the specific mortality and years of life lost due to stroke in the population.

Step 3 (non-fatal events in community) involves the collection of data on milder strokes that occur in the community. The main outcome of Step 3, when combined with results from Step 1 and Step 2, is the calculation of incidence and prevalence of stroke and of mortality and case-fatality from stroke. This is the most challenging step of STEPS-Stroke methodology.

The WHO has recommended that Step 1 should be conducted in most countries in order to obtain the minimum data needed on the burden of stroke across the world. If resources allow and central death registration is available and reliable, then all three steps should be attempted to achieve population-based stroke surveillance. Using the WHO STEPS-Stroke method, surveillance of stroke has been conducted in Sri Lanka [99] and India [12] (South Asia), Ukraine [100], Georgia [101] and Bulgaria [102] (Europe); Brazil [21] (South America), Mongolia [99] (Western Pacific); Nigeria [21] (West Africa) and Tanzania [103] (East Africa). Most studies were conducted in urban areas, while the studies in Bulgaria [102] and Tanzania [103] were conducted in both urban and rural areas. Only one study, based in urban India [12], incorporated the complete STEPS-Stroke surveillance protocol. Many of these studies did not adhere completely to the Step 1 protocols due to limited resources, particularly in respect of neuroimaging to validate diagnoses and categorise type of stroke [104]. In a recent review of data from 9 STEPS-Stroke study centres in five LMICs (India, Iran, Mozambique, Nigeria and Russia), Truelsen et al. [27] nevertheless affirmed that this method is feasible for stroke surveillance in LMICs.

Viet Nam is a LMIC with very limited resources and research capacity and, in consequence, conducting Step 2 and Step 3 of the STEPS-Stroke methodology would be impractical at first. Implementing Step 1 (hospital-based register) is a reasonable starting point for examining stroke in Viet Nam. One of the aims of this thesis, therefore, was to undertake surveillance of stroke and to estimate the incidence density of hospital-admitted stroke in the largest city of Viet Nam using Step 1 of the WHO STEPS-Stroke methodology.

Hospital-based surveillance study

As noted earlier, hospital-based data collection (Step 1, **Figure 1.3**) is considered to be feasible in LMICs [27]. By linking admission data to the catchment population served by the relevant health facilities, a hospital-based register may provide information on hospital-admitted stroke rates in the source population [27]. Hospital-based studies do have some limitations as they can only provide data on hospitalised cases. This is likely to result in under-ascertainment in HICs, but the under-ascertainment in LMICs is amplified by non-availability of diagnostic services particularly in rural areas, socio-economic factors limiting hospital access, and lack of universal healthcare. For these reasons, it is likely that patients admitted to hospital for stroke in LMICs are not representative of the entire population of stroke patients. Hospital-based studies are also limited in that they tend to under-ascertain mild cases that are not admitted to hospital, and the most severe cases that result in early death before hospital admission or home palliation without hospital admission.

The experience of population-based stroke incidence studies in HICs is that the proportion of first-ever stroke cases admitted to hospital ranges from 60% to 86% [105,106]. The

underestimation may not be uniform across all groups that suffer stroke. For example, in the 1989-90 Perth Community Stroke Study, Anderson et al. [105] reported that they would have underestimated the incidence of stroke among the most elderly patients by 40% if only cases admitted to hospital were counted. In the 1991-92 Auckland Stroke Study, Bonita et al. [96] reported that the majority (63%) of cases were ascertained from hospital admission records, while the remaining came from death registrations (10%) and general practitioners or other community-based sources (27%). A higher hospital admission rate of 86% was reported in the North East Melbourne Stroke Incidence Study (NEMESIS) conducted between 1996 and 1997 [106].

There appear to be similar differences in hospital admission rates in LMICs. For example, in India, Dalal et al. (2008) [12] conducted a study using all three Steps of the WHO STEPS-Stroke methodology in Mumbai from January 2005 to December 2006. They found that two thirds of the first-ever cases of stroke were admitted to hospitals. The remaining one third was found to be dead, treated at home or living in a nursing home. The proportion of cases admitted to hospital in other LMICs were lower. Only 46% of patients in Bulgaria [102] and 32% in Tanzania [103] were admitted to hospital. This suggests that findings derived from hospital-based stroke registries in LMICs will underestimate the true incidence of stroke in a community by at least one third and possibly by two thirds.

Nonetheless, in the setting of Viet Nam, there is a paucity of information on stroke occurrence with hospital-based studies being a feasible option to partially rectify this. There has been one previous hospital-based study of stroke using the STEPS-Stroke method in a provincial hospital in Da Nang City, central Viet Nam, from March 2010 through February 2012 [107]. In that study, nearly 50% of cases were haemorrhagic stroke (consisting of both ICH and SAH). The 28-day case fatality in the study was high at 36.4%. This study was conducted in a general public hospital without a stroke unit, and the authors noted that it was servicing a population in which the prevalence of untreated hypertension was high. The only other published data on stroke in Viet Nam come from a study conducted in the 1990s by Le at al. [108]. Those data were used as representative of Viet Nam in the recent review of Feigin et al. [2] of the global burden of stroke [2].

Comparisons of stroke occurrence between HICs and LMICs

It is important to note that summary measures of incidence of and mortality from stroke in a country may be presented as age-standardised rates. The crude rate is the summary measure of occurrence in a population. Age standardisation allows meaningful comparisons to be made between populations with different age distributions. By comparing the number of cases that would have occurred in a standard population such as the new WHO world standard population or Segi's world population or the European standard population if subject to the age-specific rates of each country being compared, the differences caused by non-identical population age structures are removed. To facilitate international comparisons, it is good practice to present both crude and age-standardised rates.

A systematic review of population-based studies of stroke incidence published from 1970 to 2008 revealed that there has been a 42% reduction in stroke incidence in HICs over the last 40 years [16]. In contrast, it was estimated that there has been more than 100% increase in stroke incidence in LMICs [16]. The overall incidence rates in LMICs was estimated to have exceeded that in HICs for the first time in 2000–08, and it did so by 20% [16].

Table 1.3: Global trends in age-adjusted annual stroke incidence per 100,000 person-years between 1990 and 2010.[*]

	High income countries		Low and middle income countries	
	1990	2010	1990	2010
Age < 75 years				
Ischaemic Stroke	110.8(103.1, 118.5)	100.5(94.0, 107.2	101.9(89.290, 116.492	106.9(93.6, 121.4)
Haemorrhagic Stroke	41.9(38.9, 45.2)	38.5(35.6, 41.2)	61.6(52.8, 71.5)	75.7(64.9, 88.7)
Total Stroke	152.7(142.3, 163.2)	138.9(130.6, 148.2)	163.5(142.4, 187.2)	182.5(158.9, 209.6)
Age ≥ 75 years				
Ischaemic Stroke	2824.4(2627.6, 3018.4)	2344.0(2197.0, 2503.8)	2367.5(2026.7, 2735.5)	2575.4(2240.7, 2850.2)
Haemorrhagic Stroke	417.5(385.9, 450.8)	380.1(351.4, 409.6)	713.8(603.3, 847.4)	859.4(729.2, 1012.6)
Total Stroke	3241.9(3020.9, 3458.8)	2724.1(2553.9, 2899.8)	3081.4(2631.0, 3562.0)	3434.8(2979.2, 3952.1)

[*] Estimates were obtained from data provided by the authors of the Global Burden of Disease Study 2010 [2,13]. Figures in parentheses present 95% confidence intervals per 100,000person-years

Table 1.3 summarises findings from Feigin et al. (2014) [1] and shows the trend in age-adjusted incidence of stroke in HICs and LMICs during the last 20 years. While the incidence of stroke in HICs decreased from 246.32/100,000 person-years in 1990 to 217.26/100,000 person-years in 2010 in HICs, the incidence of stroke in LMICs increased from 251.93/100,000 person-years in 1990 to 281.12/100,000 person-years in 2010.

Figure 1.4 provides a heat map of incidence study of stroke standardised to the WHO world population by quartiles provided by Thrift et al. [109]. Viet Nam is not featured on the map because there were no available data on incidence of stroke in Viet Nam for this period.

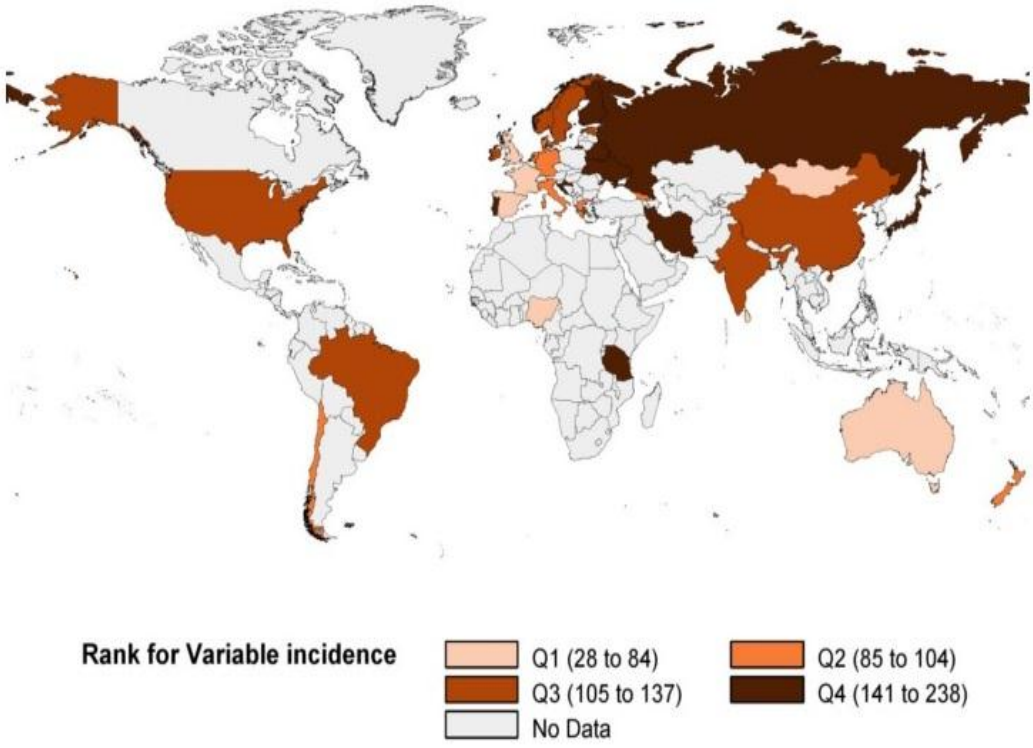


Figure 1.4: Heat map showing incidence of stroke adjusted to the WHO world population by quartiles.

Incidence of stroke in LMICs

Dalal et al. [12] used the STEP-Stroke approach to estimate the annual crude incidence density of stroke in Mumbai, India, for the period from 2005 to 2006. The incidence density estimates were 145 (95% CI 120–170) per 100,000 person-years overall, and149/100,000 person-years for males and 141/100,000 person-year for females [12]. The age-standardised rate by the direct method using Segi's 1996 world population was 152 (95% CI 132–172) per 100,000 person-years for both sexes combined. Sridharan et al. [28] reported age- and sex-standardised incidence density rates in Trivandrum, India. The estimates were 135 (95% CI 123–146) per 100,000 person-years overall, 135 (95% CI 122–148) per 100,000 person-years for the urban population with 142/100,000 for males and 130/100,000 for females in those areas, and 138 (95% CI 112–164) per 100,000 person-years for the rural population with 163/100,000 for males and 115/100,000 for females in those areas [28]. The crude annual incidence density of first-ever-in-a-lifetime stroke was estimated to be 108 (95% CI 85.7 to 134.1) per 100 000 person- years in Matao, Brazil] [21], with a rate of 136 (95% CI 101–179) per 100,000 persons-years for males and 80 (95% CI 54–114) per 100,000 person-years for females [21].

It is notable that in a recent review of stroke surveillance studies in LMICs using the WHO STEPS-Stroke approach by Sajjad et al. (2013) [104], the authors concluded that differences in estimates of age-standardised incidence of first-ever stroke between LMICs may be due to characteristics of the populations involved (urban vs rural), with differences in application of the methodology another possible contributor.

Incidence of stroke in Viet Nam

There has been only one study of the prevalence and incidence of stroke in Viet Nam. It was conducted as a door-to-door survey by Le at al. [108] in 1994/1995 in a single local community in each of the provinces of Ho Chi Minh City (urban), Tien Giang (rural) and Kien Giang (rural) in the south of Viet Nam. Overall, 54.7% of the study population was from Ho Chi Minh City. Le et al. [108] reported that the overall prevalence of stroke was 608/100,000 person-years. The incidence density estimates were 250/100,000 person-years overall, and 142/100,000 person-years in Ho Chi Minh City, 290/100,000 person-years in Tien Giang and 385/100,000 person-years in Kien Giang. The overall estimate was greater than the estimates for the same period of time (1990/1999) made for other LMICs [16]. In the recent review of the global burden of stroke by Feigin et al. [2] and Krishnamurthi et al. [13], the estimated incidence of stroke in Viet Nam was projected from the incidences made in the study of Le et al. [108] in 1994/1995. Feigin et al. [2] projected that the incidence of stroke in Viet Nam during the period 1990 to 2010 would have increased from 213.58/100,000 person-years to 254.78/100,000 person-years [2]. If incidence of stroke increased at a similar rate in Ho Chi Minh City, the community-based estimate of Le et al. [108] in 1993/1994 would have risen to 169/100,000 person-years in 2010. However, there are many assumptions and simplifications that have been made in calculating the global burden estimates. They relate to changes in incidence and population risk factors over time, both of which may result in inaccuracies in the projections of stroke incidence. The community samples were small and, in addition, there may not have been appropriate weighting of the estimates for urban and rural areas because 70% of the population of Viet Nam now lives in rural areas and more would have done so at the time. For these reasons, it is essential to obtain updated and more reliable estimates of incidence of stroke in Viet Nam

In summary, age-standardised incidence of stroke in HICs has been decreasing whereas the available evidence suggests that the incidence of stroke in LMICs has been increasing with the consequence that the age-standardised incidence of stroke in LMICs now exceeds that in HICs. However, there is a paucity of data on the occurrence of stroke in Viet Nam with which to confirm these findings apply to that country. To help fill the gap in data on incidence of stroke in Viet Nam, a hospital-based surveillance study (using Step 1 of the STEPS-Stroke methodology) was planned on the understanding that such studies are considered to be feasible in countries like Viet Nam. The results are reported in this thesis.

1.3.2. Short-term outcomes following stroke

In addition to examining the occurrence of stroke in Viet Nam by way of hospital-based surveillance, this thesis aims to describe the short-term outcomes after stroke in Viet Nam. This section outlines the different measures of outcomes after stroke onset. They include death, neurological impairment, the effects that these impairments have on the person's ability to perform everyday tasks (functional outcomes), and their impacts on the physical and emotional well-being of survivors (HRQoL).

1.3.2.1. Early stroke case fatality

Case-fatality is the most commonly assessed outcome after stroke. It is defined as the proportion of deaths due to stroke among patients with stroke during a specified period of time. **Table 1.4** summarises the findings in respect of 28-day case-fatality from previous surveillance studies conducted in LMICs. There is wide variation in the proportion of those with stroke that die within the first 28 days; however, these figures are generally higher than those for HICs (range 19-24%) [37,105,106,110,111].

Table 1.4: Summary of findings for 28-day case fatality from stroke surveillance studies conducted in LMICs.

Location	Source	Methods	Case-fatality
Bangalore, India	[26]	Population-based	20.0%
Trivandrum, India	[28]	Population-based	24.5% †
Trivandrum, India	[28]	Population-based	37.1% ‡
Mumbai, India	[12]	Population-based	29.8%
Qatar	[112]	Population-based	16.0%§
Chennai, India	[19]	Hospital-based	14.0%
Izmir, Turkey	[18]	Hospital-based	19.7%
Rural Nigeria	[11]	Hospital-based	23.8%
Iran	[113]	Hospital-based	32.0%
Northeast Malaysia	[114]	Hospital-based	34.2%
Matao, Brazil	[21]	Population-based	18.5%

†case-fatality for urban population
‡case-fatality for rural population
§case-fatality for first-ever stroke

1.3.2.2. Stroke-related neurological impairment

Neurological impairment is a loss of normal function of the neurological system. As a consequence of stroke, when the blood supply to the brain is disturbed, there is a loss of brain function that may be apparent immediately or may develop over a number of hours and days. There is a wide range of impairments and downstream functional affects from a stroke, including reduced ability to move limbs, understand or formulate speech, experience sensations or perform cognitive tasks.

The impairments causes by a stroke are measured in a neurological examination, which assesses a person's ability to carry out various tasks related to neurological function. Such examinations have been formulated into validated measurement protocols such as the National Institutes of Health Stroke Scale (NIHSS) or the Scandinavian Stroke Scale. The studies described in this thesis used the NIHSS, which is one of the most widely used measures of neurological impairments after stroke [115]. It was initially developed for use in clinical trials and has been used as a marker of stroke severity [115]. It comprises 15 items, each of which includes either a three graded (from 0 to 2) or four graded (from 0 to 3) point score range with a total score range from 0 to 42. Greater scores denote more severe neurological impairment [115]. It has acceptable reliability and validity for the assessment of neurological impairment of patients with stroke in the acute period [116-120].

1.3.2.3. Functional outcome following a stroke

Functional outcomes, which are also commonly termed disabilities or activity limitations, describe a person's ability to perform activities of daily living. These limitations of function are a result of the neurological impairments caused by the stroke

One of the instruments commonly used to measure functional outcomes after stroke is the modified Rankin Scale (mRS). This originated as the Rankin Scale (RS) in Scotland in 1957 [121] and had 5 grades representing no, slight, moderate, moderately severe and severe disability. It was designed to describe recovery from stroke at the time of discharge from hospital. The scale was modified to include measures of language and cognitive problems and renamed the modified Rankin Scale in 1998 for use in the UK-TIA study in 1988 [122]. The mRS is widely used as a measure of functional outcome after stroke [121,123-133].

The mRS has moderate inter-rater reliability for use with stroke patients [123,125]. There is some concern regarding the validity of the measure, and specifically whether it is solely measuring functional outcomes as specified in the International Classification of Functioning Disability and Health (ICF) concept [134], because the findings of some studies suggest that it also measures aspects of impairment [135,136].

The mRS has been widely used as a measure of functional status of stroke survivors in community setting. It is increasingly used in acute stage assessment of the level of disability of inpatients [137-139]. The validity of assessments made of acute stroke patients in the hospital setting has been questioned [140,141], because patient self-assessment of ability to perform "*usual duties and activities*" or "*previous activities*" or "*look after own affairs*" may be unreliable when made from the hospital bed. These descriptors are used in defining mRS grades 1 and 2. Those used in defining mRS higher grades include ability "*to walk without assistance*" and "*to attend to own bodily needs without assistance*", and being "*bedridden, incontinent and requiring constant nursing care and attention*". Those grades are more readily able to be assessed in hospital. If this prompts greater error in self-assessment by

acute-care patients than by community-based survivors, particularly by those at the lower end of the scale, the net effect may be under-reporting of least severe disability.

Although the mRS was developed in English, it is commonly used in countries with languages other than English as official language. This raises the possibility of reduced mRS reliability and validity in non-English speaking countries because the reliability and validity of the scale after translation into languages other than English has not been studied [142]. In Viet Nam, the mRS has been used commonly in clinical setting to assess the functional outcome of patients with a specific disease, such as tuberculous meningitis [143] or stroke [107,144].

Level of function during admission and in the post-acute period

It is generally reported that most functional recovery occurs within the first three to six months after stroke onset [145-149]. However, some patients may continue to experience improvements for up to 18 months after stroke [148]. In this thesis, the author examines functional outcomes measured with the mRS three months after stroke. This time point was chosen because the functional recovery of stroke survivors is stable after three months [142,150]. In studies conducted in HICs, the proportion of moderate to severe disability assessed on the mRS (mRS≥ 3) during admission has ranged from 45.7% in the Virtual International Stroke Trial Archive [151] to 73.3% in the study of Silvestrelli at al. [152] in Spain. In LMICs, this proportion has ranged from 38.5% in Mumbai, India [12] to 57.5% in Trivandrum, India [28].

Swedish data from the Riks-Stroke study showed that about 30% of stroke survivors were dependent in primary activities of daily living (ADL) at three months following stroke [153]. Glader et al. [154] showed that 57% of the patients were living at home without community support three months after stroke, and 19% were discharged to institutional living [153]. In a multicentre study conducted in Western and Central Europe, the proportions of survivors with dependent outcomes (mRS ≥ 3) ranged from 21% to 70%. In data from the Austrian Stroke Unit Registry, the proportion with moderate-to-severe outcomes (mRS ≥ 3) at three months was 37.6% [155]. Data from the Hospital-Based Perugia Stroke Registry in Italy in 2000-2003 showed that the proportion with moderate-to-severe outcomes (mRS ≥ 3) at three months was 20.9%.

In Asia, reports from studies conducted in China have shown that the percentage of patients with unfavourable functional outcomes (mRS ≥ 3) at three months were in the range 34.0-39.7% [156,157]. The finding (37.1%) of a study in Korea fell in that range [158]. There is very limited data on the level of functional outcomes of stroke survivors in LMICs after hospital discharge. In Viet Nam, only one study by Nguyen et al. [144] has reported mortality and functional outcomes and this was for patients after r-tPA treatment for acute IS. In this study, 43.0% of 121 patients with acute IS who received thrombolysis over 3 years (2006-2009) achieved independent function (mRS=0-1) and 8.3% of them were dead at three months. There is no information available on the functional outcomes after hospital discharge of patients with all types of stroke.

Predictors of severe functional outcomes at three months

There is interest in examining the factors that predict levels of function at various time points after stroke because understanding those factors could lead to strategies to improve function. The factors identified as being associated with reduced function after stroke include greater

age [159], greater severity of stroke [159], greater extent of co-morbid disease [160], pre-stroke tobacco smoking and alcohol consumption [161-164], and lower socioeconomic status [165,166].

Several studies have reported poorer outcomes for women in terms of function [24,155,167-171]. One reason may be that atrial fibrillation is related to more severe stroke [24,167,172,173] and this condition is more prevalent among women, potentially due their different age profile compared to men who suffer stroke [155,174-179]. Delay in arrival to a stroke unit has been a strong predictor of functional outcomes at three months in some studies in HICs [152,158,180,181], and some studies [32,38,182-186] but not others [25,187-190] have reported that women more often present later to hospital compared to men.

However, most of the previous studies of the factors associated with functional outcomes after stroke have been conducted in HICs. There is a lack of data from LMICs, with no such data available for Viet Nam.

1.3.2.4. Health-related quality of life after stroke onset

Quality of life (QoL) is defined by the WHO as "the perception that an individual has of his or her place in life, within the context of the culture and system values in which he or she lives, and in relation to the objectives, expectations, standards and concerns of this individual" [191]. In order to specifically relate this concept to health, WHO also defined the term health-related quality of life (HRQoL) as "an integrative measure of physical and emotional well-being, level of independence, social relationships and their relationship to salient features of their environment" [192]. This conceptualization of HRQoL recognises that HRQoL is subjective and multidimensional.

In recent years, assessment of patient-centred outcomes – such as HRQoL – has been recognised as being essential for understanding outcomes following a stroke. A multidimensional approach to assessing the HRQoL of patients with stroke should include aspects of physical, psychological, and social functioning. Multidimensional measures of HRQoL reflect spiritual and material well-being within the cultural and environmental context.

In stroke research, the increasing proportions of stroke survivors means that it is important to understand much more about their lives beyond simple measures of whether they can undertake basic tasks. HRQoL has been became an important patient-centred outcome due to the recognition that "the ultimate goal of healthcare is to restore or preserve functioning and well-being related to health, that is health-related quality of life" [193]. Relying only on assessment of clinical health status, such as determined by physician examination of neurological impairment or impaired functional status, is to ignore important factors of a patient's subjective health status. The aim of the assessment of HRQoL among patients with stroke is to determine as best as possible the impact of stroke on the patient's life and well-being. Along with traditional measurement of outcomes (such as mortality and impaired functional outcome), HRQoL is an important indicator of the burden of stroke.

HRQoL instruments

HRQoL can be measured with generic or disease-specific instruments. An advantage of a generic instrument is that its results can be compared with reference values for the general population or for patients with other diseases. However, a disadvantage of generic instruments

is that they may not measure stroke- specific dimensions such as language, cognition or vision.

There are two types of generic HRQoL instruments that are often used: health profile and utility measures. Health profile instruments include the WHO Quality of Life (WHO-QoL) [194], Short Form 36 (SF-36) [195], the Sickness Impact Profile [196], the Nottingham Health Profile [197], and the Duke Health Profile (DHP) [198]. The utility measures include the European Quality of Life (EQ-5D) [199], the Health Utilities Index [200], and Assessment of Quality of Life [201]. These instruments were developed for health economic evaluation, and can be used to calculate quality-adjusted life years (QALYs). These can be used as an outcome in cost effectiveness analyses, and are calculated by multiplying the time spent in a particular health state by the 'value' assigned to that health state.

There are instruments developed specifically to assess the HRQoL of stroke survivors. They include the Stroke Impact Scale [202,203], the Stroke Specific Quality of Life Scale [204], the Burden of Stroke Scale [205], and the Stroke and Aphasia Quality of Life scale-39 [204]. Some of them have been translated for use in non-English language countries [206-211] to assess specific relevant domains for stroke survivors.

However, among instruments used to measure HRQoL in Viet Nam, the DHP stands apart because it has been translated and culturally adapted for use among adolescents in Viet Nam. The internal consistency and the validity of the DHP were examined in a study [212] conducted in Ho Chi Minh City in the year 2000 with a sample of 1,408 adolescents selected by cluster sampling. The mean age of these adolescents was 15.7 years, and 50% of them were female. The reproducibility of the DHP was examined among 408 of the sample by retest after 2-weeks. It was found to be acceptable with intra-class correlation coefficients (ICCs) ranging from 0.7 to 0.8. Its construct validity was judged to be acceptable based on the correlations between DHP dimension scores and other study factors such as age, sex, residential location (urban or rural), family structure (family with single parent), drug use, alcohol consumption and presence of chronic disease. There are also some data available on the levels of HRQoL in the general population of Ho Chi Minh City [213], where the studies in this thesis were based. For these reasons, the DHP was selected to measure HRQoL after stroke in this study.

The DHP is a generic HRQoL instrument that was developed by researchers at the Duke University in the United States of America. It is a brief self-report instrument with good acceptability for use among the general population [198,214]. The DHP has 17 questions from which 10 domains are measured. Six of the 10 domains refer to health function (higher scores indicate better health status): physical health (five items), mental health (five items), social health (five items), general health (combining the 15 items used for the physical, mental and social health dimensions to indicate overall well-being), perceived health (single item) and self-esteem (five of the items used for the mental and social health domains). The remaining four domains refer to health dysfunction (higher scores indicate poorer health status): anxiety (six of the items used for general health), depression (five of the items used for physical and mental health), pain (single item used for physical health) and disability (single item). Each question has three possible responses scored as 0, 1 or 2. Responses to the constituent items in each domain are added and the mean of the raw scores is normalized to lie on scale of 0 (poorest health) to 100 (best possible health) for each of the 10 dimensions.

In previous studies on population samples, the DHP has been used in a study of the French general population [215] and the French adolescent population [216]. In clinical research, it

has been used for patients with cardiac failure [217], atrial fibrillation [218] and dementia [219].

The other instrument used in previous studies of HRQoL in Viet Nam was the EQ-5D. This instrument is a standardized measure of health status developed by the EuroQoL Group [199], to provide a simple, generic measure of health for clinical and economic appraisal [220-222]. It is applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single utility value. It contains the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system comprises five components: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each component has three response levels: no problems (0), some problems (1), and inability or extreme problems (2). The respondent is asked to indicate his/her health state by marking the box against the most appropriate statement in respect of each of the five components. The visual analogue scale (VAS) requires a respondent to record their self-rated health on a visual analogue scale with the endpoints labelled as "Best imaginable health state" and "Worst imaginable health state".

The EQ-5D is widely used to measure HRQoL in the general population and for patients with specific diseases including cardiovascular disease [223,224], irritable bowel syndrome [225], social phobia [226] and stroke [227]. The EQ-5D for use with stroke patients has been reported [228] to have good inter-observer agreement in all dimensions and good correlations with stroke severity and level of impairment in activities of daily living [229]. The agreement between patient and proxy assessments of HRQoL after stroke using the EQ-5D has been found to be generally acceptable (ICC> 0.70) for the EQ-5D utility score [230]. There is an officially translated version of the EQ-5D, which was used in these studies.

In Viet Nam, the EQ-5D has been used to measure HRQoL in an elderly population (> 60 years) in the FilaBavi rural community in the north of Viet Nam [231]. The EQ-5D-5L, an extended version of EQ-5D, has been used to estimate the utility score for assessing the cost-effectiveness of HIV/AIDS intervention programs in Viet Nam [232]. However, neither the EQ-5D nor the DHP have been examined for reliability or validity for use with patients with stroke in Viet Nam.

Reliability of proxy respondents for patients with stroke

Due to cognitive and communication disorders, many stroke survivors are unable to provide responses directly to self-report instruments. Asking caregivers to provide information on behalf of the patient may be preferable to excluding this highly relevant group of patients from HRQoL assessments. Agreement between stroke patients and their proxies has been shown [233] to be acceptable for generic instruments including the Sickness Impact Profile [234] and the EQ-5D [230], and for stroke-specific instruments such as the Stroke Impact Scale [235]. Nevertheless, proxies tend to report a poorer HRQoL for stroke patients than the patient self-report, particularly for physical dimensions [227,235].

Findings of studies that have assessed HRQoL of stroke survivors

<u>HRQoL of stroke patients compared with general population</u>

Most studies that have found the HRQoL of stroke patients is poorer than that of the general population were conducted in HICs [236-239]. Specifically, physical and social functions were significantly worse, on average, for stroke survivors one year post-stroke than the population norms in New Zealand [240] and Taiwan [236]. In studies with long-term follow-

up, stroke survivors had poorer physical health [238,241,242], but comparable mental health [240], to the population norms for HICs. In LMICs, the average level of HRQoL of stroke survivors at 3-6 months after stroke was lower than that of the population in studies conducted in South Africa [243] and Saudi Arabia [244].

In Viet Nam, although mean levels of HRQoL have been reported for the general adult population of the largest city of Ho Chi Minh City and for people aged greater than 60 years in a rural community in the north of Viet Nam, there has been no study of the HRQoL of stroke patients relative to the HRQoL of members of the general population.

Factors related to HRQoL after stroke

Most studies conducted in HICs have found that lower levels of HRQoL among stroke survivors are associated with greater age, being female, having lower socio-economic status, having had a more severe stroke and having poor functional status after stroke [136,239,245-247]. Studies conducted in Turkey [248], Nigeria [249], Saudi Arabia [248] and Thailand [241] have shown that, together with increasing age and severity of stroke at admission, functional status at three months has a strong influence on HRQoL of stroke patients at that time point. The first three months after stroke were found to be critical time of improvement in physical functioning and HRQoL for stroke survivors in the Asian countries of Taiwan [236,241] and Thailand [236,241]. Other factors related to poor HRQoL in the studies conducted in HICs, including comorbidity or socioeconomic status, have not been examined in studies conducted in LMICs.

Assessment of HRQoL among stroke survivors has been conducted in HICs for many years, and in some LMICs more recently. Although studies of HRQoL have been conducted in general population or persons with some specific health conditions in Viet Nam, there has been no study of HRQoL among patients with stroke in Viet Nam. This is a critical deficiency because social and cultural values may influence some specific dimensions of HRQoL assessment [250], and these may vary significantly across different populations. It is essential to assess the HRQoL of stroke survivors, and to identify factors related to their HRQoL, in the cultural and social context of Viet Nam.

1.3.2.5. Economic costs of stroke

Data from HICs suggest that stroke imposes substantial economic costs on patients, their families, healthcare systems and society [251-255]. This is mainly due to the direct healthcare costs associated with diagnosing and treating strokes, particularly during hospitalisation. There are also associated indirect costs such as the value of time lost from productive activity [252]. Studies of the cost of stroke are valuable to inform decisions about service provision and resource allocation, and to estimate the cost-effectiveness of specific interventions to prevent or treat stroke.

Methods to study the costs of stroke

Studies of cost of illness (COI) can be divided into disease specific and general studies. A disease-specific study includes all relevant costs related to a specific disease, whilst a general study includes all relevant costs for all disease categories.

Top-down and bottom-up approaches are estimation procedures used in COI studies. The top-down approach estimates costs by using aggregated data on mortality, morbidity, hospital

admissions, and general practice consultations that are usually provided centrally by public and private healthcare providers. In a bottom-up procedure, a group of patients with a specific disease is asked to provide information on the costs of their disease including cost of resources used and loss of productivity. The mean cost per person is then extrapolated to a population level [256]. In LMICs, cost related to treatment of stroke can only be assessed by a bottom-up procedure because many of the inputs for a top-down analysis – such as mortality registers and access to electronic hospital admissions or discharge data – are not available [257].

The type of costs included in a COI depends on the study perspective. The possible study perspectives include that of society, the healthcare system, third-party payers, or patients and their families. Total costs are the sum of direct costs and indirect costs. Direct costs are calculated as the sum of direct medical costs and direct non-medical costs. The direct medical costs include costs of accommodation (bed-day fees), laboratory tests, diagnostic imaging, cardiology-related investigations, medications, nursing, consultant services, and rehabilitation services in hospital [258]. Direct non-medical costs include those relating to transportation to hospital, special diets and purchasing medical aids such as wheelchairs or walking sticks. Indirect costs refer to changes in productivity resulting from illness or death, including productivity loss or time spent in treatment of the illness or being at the healthcare facility [259].

Previous findings on costs of treatment of stroke

Mean cost of stroke in HICs and LMICs

A critical review of 120 studies of cost of stroke using patient-level data conducted in countries in the Organization for Economic Cooperation and Development or the European Union [260] showed that 41% of studies included direct non-medical costs. Only a small proportion of studies included travel cost and out-of-pocket costs in the COI study. Only 9% of studies included productivity losses. After adjustment using the purchasing power parity (PPP) method to eliminate the price differences between countries, the mean cost of an acute stroke per admission was USD 19,018 (median USD 14,571), ranging from USD 468 to USD 146,149. Around 65% of overall costs were attributable to initial hospitalisation. There was an association between follow-up duration and costs, with mean costs varying from USD 10,216 at follow-up times ranging from three months to six months, to USD 28,525 one year after stroke onset. Even taking into account the differences in prices between countries, a main factor in the differences in estimated costs was the country where the study was conducted. There were, however, large differences in mean costs within the same country due to differences in cost structure between hospitals (community hospital vs provincial hospital, private hospital vs public hospital) and between different levels of stroke care (general department vs stroke unit). Other factors related to cost were length of follow up, allocated prices for use of resources rather than costs, inclusion of productivity costs and location of conducted study. Most studies of the cost of stroke are hospital-based with only 4% of studies classified as population-based. It should be kept in mind that the rate of hospitalisation for stroke and the study method (population-based or hospital-based) may affect ability to generalise the findings of a cost study to other regions of a country of other populations.

Estimates of the costs of stroke in LMICs have varied widely across different countries. **Table 1.5** summarises of average direct medical cost of stroke from a recent review of studies on cost of stroke in such countries [257]. The highest cost of stroke per case was found in

Nigeria [261] (USD 8,424), followed by Pakistan [262] (USD 5,230) and China [263] (USD 3,626). The lowest cost of stroke per case was seen in Senegal [264] (USD 416). It should be kept in mind that non-communicable diseases have a lower priority than communicable disease in LMICs [257]. This may mean that costs are underestimated in these regions because patients with non-communicable disease are not receiving optimal evidence-based care. The out-of-pocket expenditure for patients in LMICs varies from 20% to 80% of the total health expenditure [265] because governments in those countries allocate only a very small proportion of the national annual budget to health expenditure compared to that in HICs. A recent report on health expenditure by WHO in 2011 showed that health expenditure per capita was over USD 3,000 in HICs while it was only USD 30 in LMICs [266].

Table 1.5: Summary of average direct medical cost of stroke in LMICs (in USD).

			Administration type		
Country	Source	Average cost	General ward	Specific ward	ICU
Pakistan	[267]	5,230	4,488	5,538	11,465
Malaysia	[268]	2,050			
India	[269]	2,711			
China	[263]	3,626			
Thailand	[270]	2,115			
Brazil	[271]	1,624*			
	[271]	3,501**			
Argentina	[272]	3,548*	1,236*		1,759*
	[272]	3,501**	3,081**		6,600**
Turkey	[273]	2,249			
Nigeria	[261]	1,043†			
	[261]	8,424‡			
Senegal	[264]	416			

* mean cost per case with IS,** mean cost per case with ICH stroke
†mean cost per case in public hospital, ‡ mean cost per case in private hospital

In terms of resources used for stroke treatment during hospitalisation, there have been consistent findings from studies in Asian countries such as Pakistan [262], Singapore [274], South Korea [275] and Japan [276] with diagnostic imaging (32% of average costs), medications (26%) and bed-day fees (23%) the largest contributors to direct medical costs.

Factors related to costs of stroke treatment in LMICs

Some researchers have also examined the different factors that are related to the level of costs following a stroke. Identifying predictors of costs is important because doing so may detect ways that economic savings can be made. Other than studies in India [269] and Malaysia [268] in which the cost of treating ICH and IS were similar, the cost of treating haemorrhagic stroke generally has been found to be greater than the cost of treating IS in both developed and developing countries [251,263,268-270,272,277,278]. Patients with ICH are likely to have more severe stroke and longer LOS in hospital, and hence greater treatment costs for those reasons. Costs of stroke related to treatment in hospital have been found to be largely attributable to stroke severity and LOS [262,263,268-271,279,280], and positively related to the income of patients and their families in studies conducted in India [269] and China [281].

Role of health insurance

A chronic illness, such as a stroke, is a major cause of economic hardship and poverty. A prospective study of stroke [281] conducted in China found that, three months after stroke, 71% of stroke patients had experienced catastrophic healthcare payments. In that study, catastrophic healthcare payments were defined as expenditure of 30% or more of total reported household annual income [281]. One year after stroke onset, 62% patients with no health insurance fell below the poverty threshold as a result of out-of-pocket payments, compared with 23% of those with health insurance, in that study. However, in LMICs, the coverage of health insurance among stroke patients is generally low with 24% coverage reported in one study in India [269] but with 62% coverage reported in China [281]. Although there have been some studies of the direct medical costs of stroke in LMICs, there have not been any studies of non-medical and indirect costs related to hospitalisation in LMICs. In addition, there has been no study of these costs of stroke in Viet Nam.

1.4. Healthcare system in Viet Nam

Understanding the healthcare system is crucial for understanding the journey of a patient who suffers from a stroke in Viet Nam, particularly in terms of the costs associated with the stroke treatment. The Government provides public healthcare that is delivered at four levels: central, provincial, district and community [282,283] (see **Figure 1.5**, from a report of Tien et al. [283] for the health insurance system in Viet Nam).

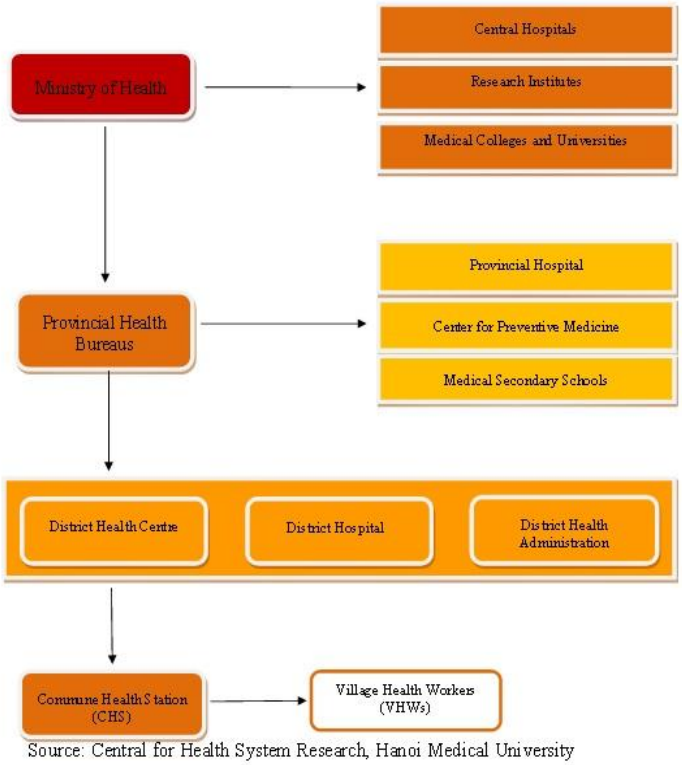


Figure 1.5: The administrative structure of the healthcare system in Viet Nam.

The district and community levels only provide primary healthcare. Specialised healthcare is mostly available at the central and provincial levels. At each of these levels, three types of public healthcare services are provided [282]:

(a) primary healthcare, preventive medicine and National Health Target Programs,

(b) population and family planning, and

(c) medical examination and treatment,

The Ministry of Health (MoH) is the main authority responsible for healthcare. It formulates and executes health policies for the whole country. The Provincial Health Bureaus, each under the jurisdiction of a Provincial People's Committee, is responsible for general administration of the provincial health system, including provincial services and the district, commune, and private services provided within the province [284]. The District Health Bureaus, each under the jurisdiction of a District People's Committee, is in charge of administering the healthcare service both at the district and community levels [284]. Commune health stations and village (commune) health workers, under the supervision of the Commune People's Committee, deliver healthcare services and carry out health programs in the community [284].

Health Insurance

Based on the Law on Health Insurance and its amendments (last updated June 13, 2014), public health insurance in Viet Nam has two schemes: compulsory and voluntary [285]. Public health insurance is compulsory for all employees. Health insurance fees, depending on categories of participants and residential areas [31], are shared between employers and employees [31]. Insured people in the community and insurance companies share the operational costs for in-patient and out-patient care with the insurers covering 30% to 100% of the cost depending on the grade of the referral hospital, with the remaining fee paid by patients as 'out of pocket' expenses. The overhead costs of the hospitals including labour costs and asset depreciation are covered by the government. The government also provides free health insurance schemes to impecunious people or those who are of ethnic minority, farmers or children under 6 years old. The coverage of public health insurance reached 66.8% in 2012 [286]. A recent report on health expenditure in Viet Nam by the World Bank Organisation showed that, during the period 2000-2011, the out-of-pocket expenditure contributed around 60% total health expenditure [287].

Figure 1.6, from a report by Somanatha et al. (2014) [287], illustrates that while the trend of health insurance coverage increased sharply from 10% in 1995 to 60% in 2010, the out-of-pocket share of total health expenditure fluctuated around 60% during this period in Viet Nam. Aiming to achieve universal healthcare in 2020, Viet Nam has been increasing the coverage of health insurance in population [288,287]. However, there has been a concern that high out-of-pocket costs may hinder achievement of the target of universal healthcare in Viet Nam.

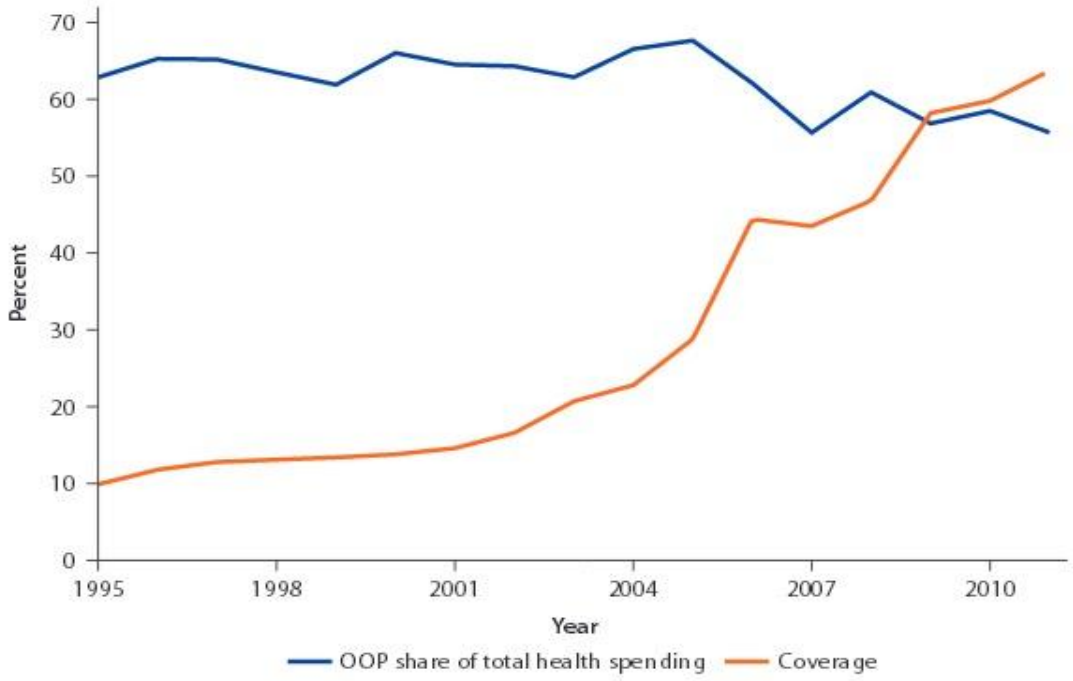


Figure 1.6: Out-of-pocket share of Total Health Expenditure and social health insurance coverage in Viet Nam during the period 1990-2011.

The 115 People's Hospital

This thesis uses data collected from stroke patients admitted to the 115 People's Hospital in Ho Chi Minh City. This provincial hospital is ranked as grade 1 general hospital based on Circular 23/2005/TT-BYT issued in 2005 [289]. Under Decision 1895/1997/QĐ-BYT [290], a grade 1 hospital is a unit of medical examination and treatment under the Ministry of Health or the Provincial Peoples' Committees. The primary function of grade 1 hospitals is to provide general medical care that consists of emergency care, medical examination and general treatment for the population in some critical provinces and cities [290]. Grade 1 hospitals are also responsible for treatment of patients who are transferred from lower grade hospitals. **Figure 1.7** from a report by Somanatha et al. (2014) [279] illustrates the National Health System Financing Flow in Viet Nam in 2010.

The 115 People's Hospital is a tertiary public hospital with 1,600 in-patient beds. It is also the main teaching hospital of Pham Ngoc Thach University of Medicine. It has had success in meeting the conditions required to operate as the first-class hospital in the city. According to the ranking guidelines for medical non-business units [285], a first-class hospital must be a leading hospital fulfilling specified criteria for medical functions, staffing, management, department structures and scales, infrastructure and facilities equipped with advanced technologies.

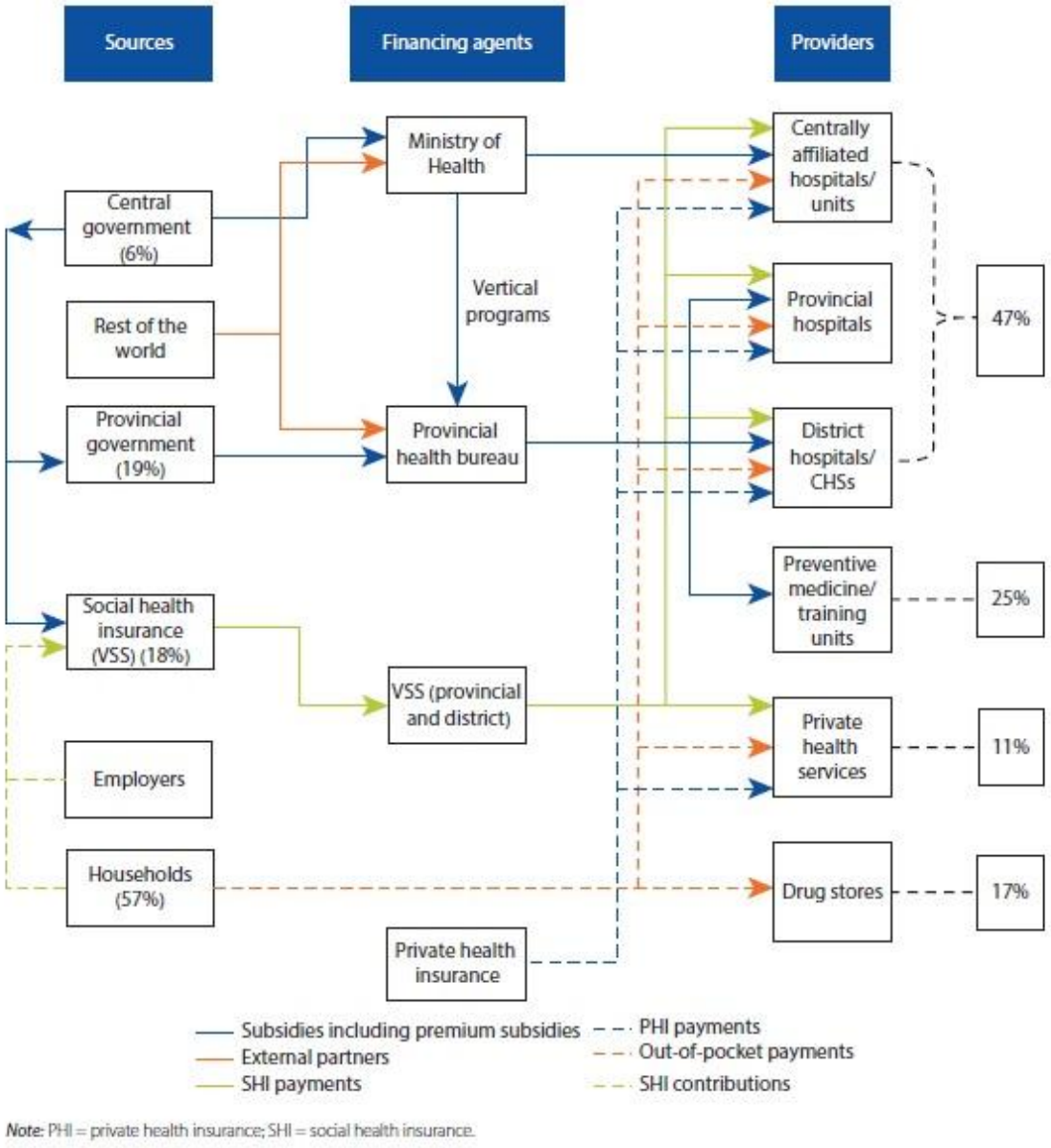


Figure 1.7: National Health System Financing Flows (2010).

Consisting of 42 offices and departments and nearly 2,000 staff, the 115 People's Hospital offers a complete range of integrated services. Its five fundamental specialist treatment fields are Neurology, Nephro-urology, Oncology-Nuclear medicine, Anaesthesia and Intensive Care (unpublished data from thee summary report of 25th anniversary of the hospital [291]). In 2012, 67,441 in-patients were admitted to the hospital and 570,959 persons received treatment as out-patients (data from report of General Planning Department of the hospital [291]). This hospital is classified in Group 3 of the health financial management system, which gives it the authority to jointly manage its regular operational funds in combination with the government's financial bodies [292].

Another role of the 115 People's Hospital in the Ho Chi Minh City healthcare system is to provide overall medical support to four lower-level hospitals located around the 115 People's Hospital: the Hoc Mon District Hospital, District 12 Hospital, District 10 Hospital and District 3 Hospital. Although it is a major provincial public hospital of Ho Chi Minh City, the

115 People's Hospital is authorised by Circular 43/2013/TT-BYT [290] to provide healthcare service to residents of adjacent provinces [290], this hospital is responsible for providing professional consultative services to general public hospitals located in rural areas of Ho Chi Minh City such as Cu Chi hospital and to other provincial hospitals such as those of Tan Tru - Long An, Dak Lak, Tien Giang, Tra Vinh, Ca Mau and Phu Yen [290].

Care of stroke in Viet Nam

There is very limited information about the level of care provided to stroke patients in Viet Nam. There are fewer than 10 stroke units across Viet Nam to service a population of more than 80 million [293], suggesting that the vast majority of patients may not receive optimal evidence-based care. Indeed, a recent report about stroke care in Viet Nam found that traditional methods such as coin rubbing or acupuncture are often the first management of stroke with only 40-50% patients transferred to hospital [293]. This is despite modern treatments such as r-tPA having been shown to be safe and feasible for use in Viet Nam [144]. Public mis-perceptions of stroke and of its treatment constitute a barrier to the wider use of modern treatments [293]. There is, therefore, an urgent need for greater public awareness of stroke as a medical emergency and greater provision of specialised care across the country. Since 2013, the Ministry of Health in Viet Nam in cooperation with the National Institute for Health and Care Excellence (NICE), an institute in the United Kingdom, has commenced to develop quality standard treatment guidelines to improve the quality of care and standardise the treatment of stroke in Viet Nam [294].

Cerebrovascular Department and Stroke Unit in the 115 People's Hospital

Patients with strokes admitted to this hospital are transferred to a specialised stroke treatment facility located in the Department of Cerebrovascular Diseases. The stroke unit was established on the 4th May 2007. The department has a general treatment facility with vascular ultrasound equipment and 100 beds, and an Intensive Care Unit (ICU) with 35 beds (9 beds with ventilators). In 2012, the overall bed occupancy rate was 104% (142/136). The Department of Cerebrovascular Diseases had 79 staff including 15 doctors, 52 nurses, 7 technicians and 5 healthcare assistants in 2012.

1.5. Summary

Stroke was ranked as the second most common cause of death and the third most common cause of disability-adjusted life-years worldwide in 2010. Although the age-standardised rates of stroke mortality have decreased in HICs and LMICs in recent years, there is a growing recognition and some evidence that the burden of stroke may have been increasing in LMICs. There is limited data on the epidemiology of stroke in LMICs including Viet Nam. The studies reported in this thesis aim to provide information for Viet Nam that will be critical for healthcare planning and health policy formulation.

1.6. Research aims and specific objectives

General aims

The general aims were to investigate the occurrence, clinical presentation, costs and three-month outcomes of stroke among patients admitted to a tertiary teaching hospital in Ho Chi Minh City, Viet Nam.

The specific objectives were:

1. To determine the frequency of stroke types, stroke severity and 28-day case-fatality.

2. To estimate the incidence density of hospital-admitted first-ever stroke in Ho Chi Minh City.

3. To investigate case-fatality and functional outcomes three months after stroke

4. To estimate the societal costs of stroke, including direct medical costs of treatment and the associated direct non-medical and indirect costs incurred during hospitalisation.

5. To assess the reliability and validity of assessments of HRQoL from patient and proxy responses to the Duke Health Profile.

6. To assess the HRQoL of first-ever stroke survivors and to identify factors related to poor HRQoL at three months post stroke.

1.7. Thesis outline

In brief, the structure of the thesis is as follows:

Chapter 1: Introduction

This chapter summarises key topics related to thesis including the clinical manifestations of stroke, the occurrence of stroke, the measurement of outcomes after stroke, and a description of the healthcare system in Viet Nam and, in particular, the hospital in which the studies reported in this thesis were conducted.

Chapter 2: Methods

This chapter provides general information on the methods used in the surveillance study (Chapter 3) and the cohort study (Chapters 4-7). Specific information on each study are included in the relevant chapter.

Chapter 3: Hospital-based surveillance of stroke over 12 months at a tertiary teaching hospital in Ho Chi Minh City, Viet Nam.

This chapter describes a surveillance study of patients with stroke admitted to 115 People's Hospital during a 12 month period to examine the age of stroke onset, type of stroke, severity of stroke at admission and 28-day case-fatality. The incidence density of hospital-admitted first-ever stroke in Ho Chi Minh City is present in this chapter. At the time of submission of this thesis, the content of this chapter had been submitted as a manuscript in consideration of publication in the International Journal of Stroke.

Chapter 4: Case-fatality and functional status three months after first-ever stroke in Viet Nam.

This chapter describes a follow-up of a cohort of 441 patients with first-ever stroke admitted to the Stroke Unit of 115 People's Hospital in Ho Chi Minh City, Viet Nam, to examine the associations between study factors (demographic factors, socio-economic factors, health status before stroke onset, lifestyle risk factors, clinical status at admission) and severity of functional status at three months. At the time of submission of this thesis, the content of this chapter have been prepared as a manuscript for submission in consideration of publication in the European Journal of Neurology

Chapter 5: Costs of first-ever stroke in Viet Nam.

This chapter reports estimates of the direct medical, direct non-medical and indirect costs during hospitalisation from 437 members of the cohort of patients with first-ever stroke admitted to Stroke Unit of 115 People's Hospital. At the time of submission of this thesis, the content of this chapter have been prepared as a manuscript for submission in consideration of publication in the Value in Health journal.

Chapter 6: Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Viet Nam.

This chapter reports an investigation of the reliability and validity of measurements of HRQoL of stroke survivors at three months made with the Duke Health Profile. The sample for this study consists of 108 of the first 135 participants in the cohort of patients with first-ever stroke admitted to Stroke Unit at 115 People's Hospital who had survived to three months, and 94 of their caregivers. At the time of submission this thesis, the content of this chapter is accepted for publication in the International Journal of Quality of Life Research [1].

Chapter 7: Health-related to quality of life among survivors three month after stroke.

This chapter reports measurements three months after stroke onset made with the Duke Health Profile and the EuroQoL EQ-5D of the HRQoL of 376 stroke survivors in the cohort of stroke patients with first-ever stroke admitted to Stroke Unit at 115 People's Hospital. At the time of submission this thesis, the contents of this chapter have been prepared as a manuscript for submission in consideration of publication in the Stroke Journal.

Chapter 8: Summary.

This chapter draws together the major findings and conclusions, summaries the contributions of the thesis, and presents recommendation for future research.

Chapter 2: Methods

2.1. Preface

The aims of this thesis were to investigate the occurrence, presentation, costs and three-month outcomes of stroke in Ho Chi Minh City, Viet Nam. The findings in respect of occurrence and presentation of stroke in this thesis were derived from hospital-based surveillance of patients with stroke who were admitted to 115 People's Hospital during the period from 9th December 2009 to 8th December 2010. To obtain information on costs related to stroke treatment in hospital and on outcomes at three months, a cohort of patients with first-ever stroke was recruited and followed over a three month period in a study conducted from 1st February 2012 to 31st December 2012. This chapter provides information firstly on the surveillance study, and secondly on the cohort study. The data obtained using the methods outlined in this chapter will be analysed in subsequent chapters.

2.2. Surveillance of stroke

The author of this thesis supervised the data collection and data management at the study site, cleaned the data, undertook the data analysis and interpretation, and drafted the manuscript reporting the results that is included as Chapter 3 of this thesis.

Background

The hospital-based surveillance of stroke was conducted as part of a larger project funded by The Atlantic Philanthropies to organise systems for surveillance of non-communicable diseases in Viet Nam. This project was a joint undertaking of the Ministry of Health of the Socialist Republic of Viet Nam and its technical advisers, the Menzies Institute for Medical Research (previously named the Menzies Research Institute and, when this study commenced, the Menzies Centre for Population Health Research) and the WHO.

In respect of surveillance of stroke, major tertiary hospitals with stroke care in Ha Noi and Ho Chi Minh City were visited by Australian project leaders to identify potential sites based on certain selection criteria. These included the quality of systems for ascertainment of hospital admissions for stroke, facilities for the treatment of stroke, and the annual average number of admission for stroke. The sites chosen were 115 People's Hospital, a major teaching hospital located in Ho Chi Minh City in the south of Viet Nam, and Bach Mai Hospital located in Ha Noi in the north of Viet Nam. This thesis presents findings of surveillance at 115 People's Hospital in Ho Chi Minh City.

Study site

115 People's Hospital was one of three tertiary hospitals (Cho Ray Hospital and Gia Dinh Hospital were the others) with stroke intensive care facilities in Ho Chi Minh City in 2007. At this hospital, the majority of stroke patients are admitted to the Stroke Unit of the Cerebrovascular Disease Department after transfer from the Emergency Department. Small numbers of patients with very severe stroke were at that time admitted to the Intensive Care Unit (ICU) or the Cardiology Department. For this study, a system for capture of data within

each of these departments in the hospital had to be devised to ensure that ascertainment of patients with stroke was as complete as possible. After the completion of this study, an Intensive Care Unit was established in 2012 for the treatment of severe stroke cases within the Cerebrovascular Disease Department.

Trialling of systems organisation and piloting of the survey was undertaken from September 2008 to August 2009. This included assessment of and improvements to methods of ascertainment of stroke admissions in the hospital, instruction and guidance in questionnaire administration, testing of follow-up processes, and training in data entry procedures. A study to examine the reliability of stroke diagnosis and recognition of neurological signs and symptoms of stroke by local physicians was conducted in the study hospital during that period. The performance of these tasks by local physicians was compared with that of an Australian specialist (Dr Velandai Srikanth) [295].

Subjects

During the 12-month period from 9th December 2009 to 8th December 2010, patients admitted with a diagnosis of stroke to the Emergency Department, ICU, the Stroke Unit of the Cerebrovascular Diseases Department, or the Cardiology Department were ascertained for possible recruitment in this study. The patients were considered for inclusion if they had been assessed by a neurologist in the ICU or Cerebrovascular Disease Department as having symptoms and signs of stroke. Confirmation by diagnostic neuro-imaging techniques – computerized tomography (CT) or magnetic resonance imaging (MRI) – was available for almost all cases. Exclusion criteria were transient ischemic attack (TIA) defined as focal neurologic symptoms lasting less than 24 hours, or discharge within 24 hours from the hospital. Ascertainment and recruitment of cases is believed to be high (greater than 90%) but this cannot be confirmed because the denominator number of eligible cases was not able to be quantified.

Study tools

This study was conducted using the Step 1 (events in hospital) protocol of "The WHO STEPwise approach to stroke surveillance (STEPS-Stroke)" survey methodology [98]. This is a standardized protocol developed by the WHO. The full protocol comprises three steps: Step 1 (events in hospital) for identifying cases of stroke admitted to hospital, Step 2 (fatal events) for identifying fatal stroke cases in the community, and Step 3 (non-fatal events) for identifying non-fatal stroke cases in the community. Details of this protocol were provided in the previous Chapter.

Two primary data collection instruments were developed. The first was the stroke log form (Appendix 2A), a simple record of stroke admissions to each department. This form captured name, age, sex, type of stroke, hospital record number and whether the patient was transferred between departments. The second was a brief questionnaire to capture essential information on demographic details, type of stroke, signs and symptoms of stroke onset, risk factors, disability and vital status 28 days post-stroke (Appendix 2B). These were developed in several iterations in conjunction with the clinicians involved, and with translation in Vietnamese and back-translation to check accuracy.

Study factors

Clinical presentation of stroke

Signs and symptoms of stroke

Stroke signs including impaired consciousness, definite brainstem signs, limb weakness, face weakness, loss of sensation, visual field deficit, neglect, aphasia/dysphasia, apraxia and ataxic gait were assessed and recorded by neurologists. Symptoms of stroke including dizziness, headache, blurred vision, double vision, slurred speech, difficulty swallowing, confusion and seizures were recorded by neurologists from self-report of patients or their caregivers.

Risk factors

Vascular risk factors for stroke including atrial fibrillation, current smoking status, diabetes, hyperlipidaemia, hypertension and valvular heart disease were assessed by the treating physician.

Type of stroke

Type of stroke including ischaemic stroke (IS), intra-cerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) was determined by neurologists using diagnostic neuro-imaging (CT or MRI).

First-ever stroke

The first-ever stroke was defined as a stroke occurring for the first time during a patient's lifetime. Previous stroke was determined by a neurologist using all available information including hospital records, neuroimaging results and self- or family-member report.

Outcome factors

Case-fatality at 28 days

Deaths due to stroke occurring in hospital and during the 28 days post-stroke onset were ascertained by telephone interview of the stroke patient or a family member to allow calculation of 28-day case fatality.

Functional status at admission

Functional status of stroke patients at admission, or soon thereafter, was assessed on the modified Rankin Scale (mRS) by a neurologist. The mRS scores are a grading of disability in six levels [122] ranging from 0 (normal) to 6 (death). For further details of this instrument, refer to section 3 of Introduction.

Hospital-admitted incidence density

The incidence density of hospital-admitted stroke was estimated from the number of patients with a first-ever stroke who were Ho Chi Minh City residents and had provided a residential address that could be geocoded to a ward of Ho Chi Minh City, and with the total of the populations of those wards as the denominator. The population data were provided by the General Statistics Office from Census data for 2010.

Data collection

The log form (Appendix 2A) was filled in by nurses or physicians working in each department. The questionnaire (Appendix 2B) was completed by a treating physician in the Stroke Unit (one of 14 physicians) or ICU (one of two physicians). The treating neurologist assessed functional status of patients at admission using the mRS. Research nurses in the Stroke Unit contacted patients or their caregivers by telephone 28 days post-stroke to collect data on vital status, and entered data into the database.

Data management

Hard copies of the log forms and questionnaires were collected weekly from the sites and stored in locked filling cabinets in the Cerebrovascular Disease Department, 115 People's Hospital. EpiData was used as a database to store data entered from the log forms and questionnaires. Data entry was conducted by research nurses. The data file was sent fortnightly to the Menzies Institute for Medical Research where it was checked for inconsistencies and potential errors, and with results communicated to the site for action or verification where necessary.

When all data entry was completed, data cleaning – particularly to identify duplicate records (of which there were around 10,000), to identify missing data and to replace with complete data where possible, and to correct errors – was undertaken at the Menzies Institute for Medical Research by the author of this thesis.

2.3. Cohort of patients with first-ever stroke

The research reported in Chapters 4–7 of this thesis was conducted as a part of the follow-up to three months of a cohort of patients with first-ever stroke that was conducted from 1st February to 31st December, 2012. The author of this thesis participated in the design of the study, including by advising on appropriate methods of recruitment and determining the sample size required, and prepared the ethics applications submitted to the Tasmanian Health and Medical Human Research Ethics Committee, and to university and hospital ethics committees in Viet Nam. The author contributed to the design of questionnaires and data collection instruments, created written study protocols to standardise data collection in the field, recruited and trained the research staff who undertook the fieldwork, piloted and modified the methods of participant recruitment, and revised the questionnaires and data collection instruments in light of the pilot study experience. When the actual study was conducted, the author participated in the recruitment of participants, supervised data collection in the hospital and at the subsequent three-month follow-up in each patient's home, contributed to the design of the database, supervised data entry and management (secure storage of the data in electronics files), and performed data linkage to the electronic administration system at the hospital to extract information on hospital costs. In addition, the author was involved in preparing budgets and monitoring research expenditure against budget.

The author's supervisors – Associate Professor Leigh Blizzard, Associate Professor Velandai Srikanth and Dr Seana Gall – assisted in designing the study and supervising data collection in the field (by weekly teleconference with the author while the study was being conducted in Viet Nam). Associate Professor Velandai Srikanth, a specialist senior geriatrician with clinical

expertise in stroke, helped to train the research staff in assessment of functional status using the mRS. Dr Vo T.X. Hanh, who translated the DHP for first use among the adolescents in Ho Chi Minh City and assessed its validity for that purpose, helped to train research staff in the assessment of HRQoL using the DHP. Two research nurses in the Stroke Unit of the hospital assisted the author to identify patients with stroke admitted to the Cerebrovascular Disease Department each day, and to extract information on hospital fees from the database of hospital administration system. All stroke neurologists (14 physicians) in the department participated in the study by helping to complete the sections of the in-hospital questionnaire requiring clinical details. Data collection in hospital and during the three month follow up were conducted by four research staff (who were general practitioners) in the pilot study, and by five research staff (who were either general practitioners or medical students) in the actual cohort study.

Study design

This was a prospective study of a cohort of patients with first-ever stroke who were treated in the Stroke Unit of 115 People's Hospital, Ho Chi Minh City, Viet Nam.

Study population

The study population consisted of patients with first-ever stroke who were residents of Ho Chi Minh City, Viet Nam.

Study sample

The study sample consisted of 450 patients admitted to the Stroke Unit at 115 People's Hospital during the period from 1st June 2012 to 10th September 2012 with a diagnosis of stroke confirmed by a neurologist working in Cerebrovascular Disease Department of the hospital.

The study inclusion criteria were (1) definitive stroke meeting the WHO definition, (2) age greater than 16 years, (3) first-ever stroke, (4) stroke occurrence within the past 7 days, (5) treatment of stroke in the Cerebrovascular Disease Department, and (6) residence in Ho Chi Minh City.

Study factors

As described in Chapter 1, factors that have been found to be predictors of poor outcomes after stroke onset are advancing age, female sex, lower socioeconomic status, disability prior to stroke, comorbidity, ICH type of stroke, severity of stroke and severity of disability. They were the study factors that were measured in this study.

Demographic and socioeconomic information

Age

In this study, patient age was calculated by deducting the patient's year of birth from the year of their stroke onset.

Education

Education in Viet Nam is classified into five levels: preschool, primary school (grades 1-5), secondary school (grades 6-9), high school (grades 10-12) and higher education. Formal education consists of twelve years of basic education (five years of primary education, four years of intermediate education, and three years of higher education). For this survey, education level attained was self-reported or reported by caregivers as no schooling, primary school not completed, completed primary school, completed secondary school, completed high school, TAFE, university, post-university and unknown.

Working status

Working status was determined from self-report or report by caregivers of type of work performed, and was grouped into the three categories of manual work, office work and home duties/retired.

Living arrangements

Living arrangements were self-reported or reported by caregivers with six response options that were combined into the three categories of living with spouse, not living with spouse but living with offspring, and living with others (not living with spouse or offspring).

Socio-economic status

Socio-economic status was assessed as a wealth index based on the holdings, in the household of each patient, of assets included in the list of 2010 for Ho Chi Minh City published by the General Statistics Office of Viet Nam. A weighted sum of the assets held was calculated, with weights derived from the linear regression of household expenditure on binary (0=asset not held / 1=asset held) predictors for each asset in the list. Information on the average monthly income from the main source of income (main salary) and from other sources (such as rent, personal business income or bank interest) was collected for each patient's household, together with average monthly expenditure of the household and the average number of persons living in the household. Patients or their caregivers were asked to provide information on the source of payments made for costs that were related to stroke and were incurred during the hospital stay.

Health insurance

Health insurance status was recorded from information contained in each patient's hospital medical record.

Lifestyle factors

Cigarette smoking

Smoking status (never, former or current) was determined from the responses of patients or their caregivers to the questions "Have you ever used tobacco in your life?" and "Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes?". Participants were considered a current smoker if they reported that they currently smoked any tobacco products. If the participant was a current smoker or an ex-smoker, information on average daily number of cigarettes and number of years of smoking was collected.

Alcohol consumption

Alcohol consumption was determined from the responses of patients or their caregivers to the questions "Have you ever consumed an alcoholic drink such as beer, wine, spirits, fermented cider?", "Have you consumed an alcoholic drink within the past 12 months?" and "During the past 12 months, how frequently have you had at least one alcoholic drink?". For those who had consumed alcohol during the past 12 months, information was collected on the frequency with which alcohol was consumed, the average amount of alcohol (number of standard drinks) consumed per occasion and types of alcohol consumed. Visual representations (showcards) were used to illustrate a typical serving size that amounted to one standard drink such as a glass of beer (285 ml), a glass (120 ml) of wine or a small cup (30 ml) of spirit (see Appendix 2G).

Health status prior to stroke

Disability prior to stroke

Disability prior to stroke was determined from the responses of patients or their care-givers to the questions "Before stroke onset, did patient have limited functional status (disability)?" and "If yes, please give details of the type and severity of disability".

Co-morbidities

Patients were asked whether they had been told by a health worker that they had high blood pressure or diabetes, whether they had received treatment for those conditions, and whether they had had their blood pressure and blood glucose measured during the last 12 months. They were asked also whether they had chronic heart disease, lung disease, kidney disease, liver disease or cancer, and whether they had had a stroke in the past.

Outcome factors measured

The outcome factors measured were case fatality, functional status, health related quality of life at three months after stroke onset, and costs of treatment during the hospitalisation.

Case fatality

Case fatality was defined as the death of a study participant during the study period (three months). Information on deaths occurring in-hospital was collected from hospital administration records. Information on deaths occurring out-of-hospital during the following three months was provided by caregivers or family members. Case fatality is reported as a percentage after dividing the number of deaths by the total number in the cohort and multiplying by 100.

Functional status

Functional status was assessed on the mRS [122] that grades functional impairments with scores ranging from 0 (no symptom) to 6 (death). Functional status was assessed at the time of hospital admission or soon thereafter by a stroke neurologist in the Cerebrovascular

Disease Department. It was assessed again at three months post-stroke by research assistants during an interview conducted in each patient's home.

Health-related quality of life

Health-related quality of life was measured using two generic instruments: the Duke Health Profile (DHP) (Appendix 2C) and the EuroQoL EQ-5D-3L (Appendix 2D) The DHP was translated and culturally adapted for use with adolescents in Viet Nam [212], and had been used to measure HRQoL of members of a general adult population sample in Ho Chi Minh City, Viet Nam [213]. The official Vietnamese version of the EQ-5D was obtained from the EuroQol group. In the absence of a value set for Viet Nam, the values for South Korea were used [296]. The reliability and validity of these instruments in stroke is assessed in chapter 6.

Costs of treatments

Direct medical costs refer to the cost of medical resources used in stroke treatment during the hospital stay. The number of each kind of medical resource used, and its unit cost, were extracted from the electronic records of the hospital administration system. For patients with health insurance, the medical costs invoiced to patients and the health insurance co-payment were itemised.

Direct non-medical costs included transportation fees, cost of food for patients or caregivers and other sundry expenses incurred during the hospital admission. This information was collected from reports of patients or their caregivers.

Indirect cost included any loss of income of patients and their caregivers. It was estimated by multiplying the average daily income of the patient or caregiver by the number of days spent in the hospital. Information on income was self-reported by patients and their caregivers. Length of stay was extracted from hospital administration records.

Study tools

The study questionnaires were designed for this project by the author and were revised to take account of factors identified in the pilot study. The questions on cigarette smoking and alcohol consumption were modified from those used in "The WHO STEPwise approach to surveillance of non-communicable diseases (STEPS)" questionnaire developed by WHO [98]. The questions on the non-medical and indirect costs of treatment of stroke were adapted from the questionnaire developed previously by the author for a study of the costs of traumatic brain injury in Viet Nam [297]. The study questionnaires included an in-hospital questionnaire and a three-month follow-up questionnaire.

The in-hospital questionnaire

The in-hospital questionnaire (Appendix 2E) had two components. The first component was used to gather information on demographic and socio-economic factors and health status prior to stroke. It was administered by research staff in a face-to-face interview of patients or their care-givers. The second component was used to record information on the clinical presentation (type of stroke, severity of stroke and functional status) of each stroke patient. It was completed by a stroke neurologist.

The three-month follow-up questionnaire

The follow-up questionnaire (Appendix 2F) included questions to assess functional status and health-related quality of life of the patient three months after stroke onset. It was used also to collect data on costs incurred during the three months following stroke. Costs incurred after discharge from the hospital are not reported in this thesis.

Data collection

At baseline

Each day, the research nurse identified from the electronic records of the administration system of the hospital all patients with stroke who had been admitted to the Cerebrovascular Disease Department. The author selected eligible participants by obtaining and matching information from the medical records on those patients who met the study inclusion criteria. The name of each patient who met the study inclusion criteria was notified to their treating stroke neurologist in the Stroke Unit. The neurologist introduced each eligible patient or their caregiver to research staff who explained the purposes of the study. If the patient or caregiver agreed to be involved in the study, the patient or their next-of-kin was given a consent form and the participant information sheet.

Research staff then briefly interviewed the patient or their next-of kin to obtain demographic information, contact details, basic medical history, and information about health-related behaviours such as tobacco smoking and alcohol consumption prior to stroke onset. Information on non-medical costs – such as that of family care, food, transportation and loss of income – were gathered daily by self-report from patients or their caregivers during the hospital stay. After participants had completed stroke treatment and had been discharged from the hospital, the research nurse extracted information on hospital medical costs from the electronic records of the hospital administration system.

Follow-up at one month and two month

At one month and two months after stroke, patients or caregivers were contacted by telephone (call duration approximately 5-10 minutes) to collect data on vital status. Date of death of decedents was recorded at these times.

Follow-up at three months

Three months after the stroke onset, research staff visited patients in their homes to record information on their functional status and HRQoL. If the patient had a very severe cognitive impairment or difficulty communicating, their main caregiver was asked to provide information on their behalf as their proxy. This visit took around one hour to complete.

Time frames for the pilot and main studies

A pilot study was conducted prior to the main study. Stroke patients in the hospital who met eligibility criteria were recruited during the period from 1st February to 28th February 2012. They were followed up during the three months from March 2012 to May 2012. The study procedures and processes of data collection were evaluated, and revisions to them were made during the period from February 2012 to May 2012 by the main investigators.

Recruitment for the main study commenced on 1st June 2012 and continued until 10th September 2012. Three-month follow up was conducted during the period commencing on 1st September and was completed on 31st December 2012.

Data management

EpiData version 3.1 was used by research staff to enter data under the supervision of the author. Double-entry of 10% of questionnaires was undertaken to check the accuracy of the data entry process. All hard copies of questionnaires, including those used at baseline and for the three-month follow-up, were scanned and stored in electronic files.

After completing data entry, the data files were exported to Stata software version 12.0 (Statacorp, College Station, Texas, USA) for cleaning and linking to the database containing information on medical costs that had been extracted from the electronic records of the hospital administration system.

Data analysis

Methods of data analysis for each individual study are reported in the relevant chapters of this thesis.

Sample size for the outcomes analyses

In the hospital-based surveillance study, around 300 stroke patients were admitted to 115 People's Hospital per month. Of the total number admitted, 70% were residents of Ho Chi Minh City and 75% had had a first-ever stroke, and 12.2% with confirmed vital status were deceased at 28 days.

The power calculations that follow are based on a final sample of n = 300. As shown in the next section, this number provides at least 80% power to detect in most cases the differences in key outcomes observed in other studies.

Assuming that loss to follow-up (deaths and withdrawal) could be as high as 33%, 450 patients would need to be recruited to obtain a sample of n = 300 at the three-month follow-up. This would require around three months of recruitment of Ho Chi Minh City residents with first-ever stroke. A recruitment period of around three months was judged by the author to be feasible.

As events transpired, however, there was less loss to follow-up than anticipated. Information was available at follow-up for 376 survivors. That total included 328 patients interviewed in person, and 48 persons for whom information was provided by a proxy respondent (17% of the proxy respondents were a spouse and 71% of the proxy respondents were a child.

Statistical power for the outcomes analyses

The tables below show the differences in proportions or means that could be detected with 80% power (two-sided α=0.05) in a group of 300 stroke survivors at three months classified

by relevant study factors. The calculations are based on the method of Rosner [298] for means, and Fleiss et al. [299] for proportions, as implemented in Stata command *sampsi.*

Case fatality at three months

Based on frequencies of the study factors (sex, age and type of stroke) in the hospital-based surveillance study conducted in the same study hospital, and the three-month case fatality reported in previous studies [300,301], the minimal detectable differences (MDDs) in case fatality are shown in Table 2.1. A sample size of $n = 300$ would provide at least 80% power (two-sided $\alpha=0.05$) to detect the difference in three-month case fatalities for age and type of stroke found in previous studies.

Table 2.1. Minimal detectable difference in case fatality at three months.

Study factor	Expected frequency of study factor*	Expected prevalence of outcome†	Source	MDD in prevalence of outcome‡
Sex				
Males	54.2%	15.2%	[300]	15.2%
Females	45.8%	20.2%	[300]	28.7%
Sex				
Males	54.2%	14.8%	[301]	14.8%
Females	45.8%	21.0%	[301]	29.2%
Age				
Less than 65 years	51.7%	6.9%	[301]	6.9%
65 years or greater	48.3%	22.8%	[301]	18.2%
Type of stroke				
Ischaemic stroke	78.8%	20.1%	[110]	20.1%
Intra-cerebral haemorrhage	21.2%	50.0%	[110]	38.4%

* Frequency of this study factor in the stroke surveillance study.
† Prevalence of the outcome in this group reported in the source study.
‡ MDD with 80% power (two-sided $\alpha=0.05$) if prevalence of the outcome at the first-named level of the study factor is as reported in the source study.

Functional outcomes at three months

There are several different instruments used to measure functional status, and the proportions with good functional status reported in previous studies differ from study to study according to the measure used. In Table 2.2, results are reported for three different definitions of good functional status: mRS ≤ 3 by Gargano et al [300] in respect of differences by sex, as Barthel Index ≥ 95 by Eriksson et al. [302] in respect of differences by sex and age, and as mRS < 3 by Hong et al [303] in respect of differences by grade of stroke severity. Based on the frequency of those study factors found in the hospital-based surveillance study conducted in the same study hospital, a sample size of $n = 300$ would provide at least 80% power (two-sided $\alpha=0.05$) to detect the differences in three-month good functional outcomes by level of study factors in previous studies other than the difference by sex reported by Gargano et al. [300].

Table 2.2. Minimal detectable difference in prevalence of good functional status at three months.

Study factor	Expected frequency of study factor*	Expected prevalence of outcome†	Source	MDD in prevalence of outcome‡
Sex				
Males	54.2%	81.0%	[300]	81.0%
Females	45.8%	76.1%	[300]	66.5%
Sex				
Males	54.2%	68.8%	[302]	68.8%
Females	45.8%	49.4%	[302]	52.4%
Age				
Less than 60 years	37.7%	65.9%	[302]	65.9%
60 years or greater	62.3%	53.3%	[302]	48.8%
Severity of stroke				
Less severe (mRS < 3)	22.5%	80.0%	[303]	80.0%
Severe (mRS ≥ 3)	77.5%	31.6%	[303]	61.4%

* Frequency of this study factor in the stroke surveillance study.
† Prevalence of the outcome in this group reported in the source study.
‡ MDD with 80% power (two-sided α=0.05) if prevalence of the outcome at the first-named level of the study factor is as reported in the source study.

Level of HRQoL at three months

Table 2.3 shows that a sample size of *n* = 300 would provide at least 80% power (two-sided α=0.05) to detect the differences in mean HRQoL score of stroke survivors between subjects with less severe and most severe (mRS> 3) disability reported in a previous study (13). The actual sample size of *n* = 376 that was attained would make it possible to detect the difference by age reported by Abubakar and Isezuo [249]. In the source studies, HRQoL was measured on the Stroke Impact Scale by Abubakar and Isezuo [249], with the Stroke-Specific QoL instrument by Kim et al [304], and with the SF-36 by Rachpukdee et al [241].

Table 2.3. Minimal detectable difference in health-related quality of life at three months.

Study factor	Expected frequency of study factor*	Expected mean (SD) of outcome†	Source	MDD in mean of outcome‡
Sex				
Males	54.2%	70.8 (13.8)	[249]	70.8 (19.0)
Females	45.8%	66.8 (23.7)	[249]	64.7 (19.0)
Age				
Less than 45 years	6.8%	4.47 (0.62)	[304]	4.47 (0.84)
45 years or greater	93.2%	4.00 (0.85)	[304]	3.93 (0.84)
Severity of disability				
Less severe (mRS ≤ 3)	48.1%	33.6 (23.3)	[241]	33.6 (46.2)
Most severe (mRS = 4/5)	51.9%	75.0 (60.0)	[241]	48.6 (46.2)

* Frequency of this study factor in the stroke surveillance study.
† Mean and standard deviation (SD) of the outcome in this group reported in the source study
‡ MDD with 80% power (two-sided α=0.05) if the mean of the outcome at the first-named level of the study factor is as reported in the source study and the variances are pooled.

Costs of stroke

Table 2.3 shows that a sample size of n = 300 would thus provide at least 80% power (two-sided α=0.05) to detect the differences in mean costs by level of study factors reported in previous studies.

Table 2.4: Minimal detectable difference (MDD) in costs of stroke.

Study factor	Expected frequency of study factor*	Expected mean (SD) of outcome†	Source	MDD in mean of outcome‡
Age				
Less than 65 years	51.7%	£13,250 (11,228)	[305]	£13,250 (9,545)
65 years or greater	48.3%	£10,170 (7,322)	[305]	£10,180 (9,545)
Severity of stroke				
Less severe (mRS= 0-2)	22.5%	£10,149 (7,826)	[305]	£10,149 (11,310)
Severe (mRS ≥ 3)	77.5%	£14,650 (12,135)	[305]	£14,496 (11,310)
Type of stroke				
Ischaemic stroke	77.4%	$3,888 (4,018)	[272]	$3,888 (7,663)
Intra-cerebral haemorrhage	20.8%	$12,285 (14,336)	[272]	$12,285 (7,663)

* Frequency of this study factor in the stroke surveillance study.
† Prevalence of the outcome in this group reported in the source study
‡ MDD with 80% power (two-sided α=0.05) if the mean of the outcome at the first-named level of the study factor is as reported in the source study and the variances are pooled.

Sample size and statistical power for the reliability study

The first 135 patients alive at three months (including 55 participants in the pilot study, and the first 80 from the main study) were requested to participate in a reliability study that involved re-administration of the health-related quality of life questionnaires (the DHP and EQ-5D) one week later. The caregivers of these patients were also asked to complete again the DHP questionnaire for assessment of proxy-patient reliability.

In their analysis of the reproducibility of assessments of HRQoL of adolescents in Ho Chi Minh City using the DHP, Hanh et al. [212] reported values of the intra-class correlation (ICC) in a single replication study in the range 0.72 – 0.80. Based on the tables provided by Walter et al. [306], a sample of 100 subjects for a single replication study would provide 80% power (one-sided α=0.05) to detect an ICC of 0.74 as being larger than 0.6 (a plausible benchmark value). In the classification system of Landis and Koch [307], values in the range 0.41 – 0.60 represent moderate agreement. Hence a sample size of 100 would provide adequate power to conclude that values of the ICC of at least 0.74 – within the range reported by Hanh et al. [212] – represent better than moderate agreement.

Ethics

Ethics approvals to conduct these studies were obtained from the Tasmanian Health and Medical Human Research Ethics Committee and from the local ethics committees of Pham Ngoc Thach University of Medicine and 115 People's Hospital. Written consent was obtained from each of the participants.

2.4. Postscript

This chapter has provided information on the methods used for collecting and managing data on the occurrence, presentation, costs and three-month outcomes of stroke. The chapters that follow provide the results of studies using those data to address the aims of this research. Specifically, Chapter 3 presents results of the stroke surveillance study in respect of the occurrence and hospital-based incidence of stroke in Ho Chi Minh City, Viet Nam. The remaining chapters utilise data from the cohort study of first-ever stroke to provide results in respect of the case fatality and functional status at three months post stroke (Chapter 4), the costs of treatment of stroke during the hospital admission (Chapter 5), the reliability and validity of the Duke Health Profile to measure HRQoL of stroke patients in Viet Nam (Chapter 6), and HRQoL of stroke survivors at three months post stroke (Chapter 7). A summary of, and conclusions drawn from the research, are provided in Chapter 8 together with directions for future research.

Appendix 2A: Log form of stroke registry in hospitals in Viet Nam

Name	**Gender**	**Age**	**Year of Birth** (e.g. 1965)	**Hospital Record No.**	**Date of Admission** DD/MM/YYYY	**If Died in Hospital, Date of Death** DD/MM/YYYY	**Transferred to which ward**	**ID allocated**	**Date of stroke,** DD/MM/YYYY	**Type of stroke diagnosed** (Ischaemic stroke; ICH; SAH)
					/ /	/ /			/ /	
					/ /	/ /			/ /	
					/ /	/ /			/ /	
					/ /	/ /			/ /	
					/ /	/ /			/ /	
					/ /	/ /			/ /	
					/ /	/ /			/ /	

Appendix 2 B: Stroke survey questionnaire in hospitals in Viet Nam

Patient ID
Fill ID | | | | | | **I1**

Stroke surveillance site code
Fill code | | | | | **I2**

Hospital record ID | | | | | | | | | | **I3**

Information of patient

Patients Full Name
[_____] I4

Patient common name
[_____] I5

Contact home phone number
[_____] **I6**

Contact mobile phone number
[_____] **I7**

Address
[_____] **I8**

Address
[_____] **I9**

<u>Demographic information of patient</u>

Age | | | | **I10**

Gender*[choose onet]*
Male (1)
Female (0) | **I11**

Date of stroke onset
(Write date that symptoms were first noticed)

| | | | | | | | **I12**
Date Month Year

Did patient have another stroke prior this stroke?

Yes (1)
No (0)
Insufficient data (9) | **I13**

RECORDED CLINICAL MANIFESTATION OF STROKE FROM PHYSICIAN

Did the symptoms happen suddenly? *[select one]*	Yes No Insufficient data	(1) (0) (9)	☐	**I14**
Side of the body affected? *[Select one]*?	Left Right Both Unknown	(1) (2) (3) (9)	☐	**I15**

What were the symptoms and signs at stroke onset? *[Fill 1 for YES, 0 for NO, or 9 for UNKNOWN]*

Symptoms			**Signs**		
Dizziness	☐	**I16**	Impaired consciousness	☐	**I24**
Headache	☐	**I17**	Definite brainstem signs	☐	**I25**
Blurred vision	☐	**I18**	Limb weakness	☐	**I26**
Double vision	☐	**I19**	Face weakness	☐	**I27**
Slurred speech	☐	**I20**	Loss of sensation	☐	**I28**
Difficult swallowing	☐	**I21**	Visual field deficit	☐	**I29**
Confusion	☐	**I22**	Neglect	☐	**I30**
Seizures	☐	**I23**	Aphasia/dysphasia	☐	**I31**
			Apraxia	☐	**I32**
			Ataxic gait	☐	**I33**

Assessment disability on modified Rankin Scale

Assign a score from 0 to 6 for the severity of disability when first seen in hospital *[select onet]*:

No symptoms	(0)	☐	**I34**
No significant disability despite symptoms,	(1)		
Slight disability,	(2)		
Moderate disability	(3)		
Moderately severe disability	(4)		
Severe disability	(5)		
Dead	(6)		

Classification of stroke

What type of stroke is diagnosed? *[chọn một]*

Ischaemic stroke	(1)	☐	**I35**
Intracerebral haemorrhage	(2)		

Subarachnoid heamorrahage	(3)
Undetermined	(4)

If the answer to I35 was 1, go to I36. If the answer to I35 was 2, 3, 4 go to I37

What is the presumed mechanism of stroke? **I36**

Large artery atherosclerosis	(1)
Cardioembolism	(2)
Small artery occlusion	(3)
Determined, other aetiology	(4)
Undetermined	(9)

Which of the following vascular risk factors is the patient known to have? *[1=YES, 0=NO, 9=UNKNOWN]*

Atrial fibrilation	**I37**	Hyperlipidaemia	**I40**
Current smoker	**I38**	High blood pressure	**I41**
Diabetes	**I39**	Valvular heart disease	**I42**

****

<u>Follow-up the patient at 28th day after stroke</u>

Was it possible to follow-up the patient at day 28th after stroke? *[select one]* **I43**

Yes	(1)
No, no contact	(2)
No, patient refused	(3)

What was vital status of the patient at 28th day?*[select one]*
Use "i=unknown" if no follow-up completed **I44**

Alive	(1)
Dead	(2)
Unknown	(9)

Date of death? Day Month Year

Appendix 2 C: The Duke Health Profile

Revised version 19/09/04

ADOLESCENT DUKE HEALTH PROFILE (THE DUKE)
(Adolescent's Duke Scale in Vietnamese)

INSTRUCTIONS : Here are some questions about your health and feelings. Please read each question carefully and check (√) your best answer the questions in your own way. There are no right or wrong answers.

	Yes, describes me exactly	Somewhat describes me	No, doesn't describe me at all
1. I am satisfied with myself	☐	☐	☐
2. I am not an easy person to get along with	☐	☐	☐
3. I am basically healthy person	☐	☐	☐
4. I give up too easily	☐	☐	☐
5. I have difficulty concentrating	☐	☐	☐
6. I am happy with my family relationships	☐	☐	☐
7. I feel at ease being around people	☐	☐	☐

TODAY : Would you have any physical trouble or difficulty

	None	Some	A lot
8. walking up a flght of stairs	☐	☐	☐
9. Running the legth of 100 meters or the distance between three light poles	☐	☐	☐

DURING LAST WEEK : How much trouble have you had with

	None	Some	A lot
10. Sleeping	☐	☐	☐
11. Hurting or aching in any part of your body	☐	☐	☐
12. Getting tired easily	☐	☐	☐
13. Feeling depressed or sad	☐	☐	☐
14. Nervousness	☐	☐	☐

DURING LAST WEEK : How often did you

	None	Some	A lot
15. Socialize with other people (talk or visit with friends or relatives)	☐	☐	☐
16. Take part in social, religious or recreation activities (meetings, church, pagoda, movies, sports, parties)	☐	☐	☐

DURING LAST WEEK : How often did you

	None	1-4 days	5-7 days
17. Stay in your house or hospital because of sickness, injury, or other health problem	☐	☐	☐

Appendix 2 D: The Euro-QoL (EQ-5D) and Visual analogue scale

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

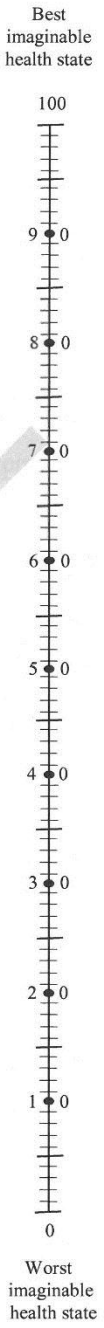
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 2 E: In-hospital questionnaire

PART 1: PATIENT INFORMATION FROM MEDICAL RECORD			Code
1	Survey Assistant Code		1
2	Patient ID		2
3	Hospital medical record number		3
4	Admission record number		4
5	Patient Full Name		5
6	Date of birth		6
7	Sex Male (1) Female (2)		7
8	Address		8
9	Date of filling questionnaire		9
10	Date of admission in hospital (hour/day/month/year)		10
11	Date of admission to stroke unit) (hour/day/month/year)		11
12	Time of stroke onset		12
13	At admission time		
	Pulse		13
	Blood pressure		14
	Glycemie		15
	Triglyceride		16
14	NIHSS score at admission		17
15	mRS at admission		18
16	Type of stroke IS (1) ICH (2) Unknown (3)		19
17	Does patient have health insurance? Yes (1) No (2) Unknown (3)		20
18	If yes, which type of insurance Mandatory (1) voluntary (2) private (3) other (4)		21
	If yes, give proportion of insurance co-payment		22

PART 2: FROM INTERVIEW PATIENTS			
19	Ethnicity Kinh (1) Chinese (2) Other (3)		23
20	Marital status Married (1) Single (2) Divorce (3) Widowhood (4)		24
21	With whom is patient living Spouse (1) Siblings (2) Offspring (3) Parents (4) Friends (5) Others (6)		25
22	Education level No school (0) Not complete primary school (1) Complete primary school (2) Complete secondary school (3) Complete high school (4) TAFE (5) University (6) Post University (7) Unknown (8)		26
23	Career status Manager (1) Professional including teacher, doctor (2) Officer (3) Service including hotel, restaurant, security (4) Sale or simple manual work (5) Farm (6) Forest (7) Fish/seafood (8) Mineral (9) Builder (10) In industry (11) Operator (12) Driver (13)		27

	Student (14) Housewife (15) Retired (16) Unknown (17)		
24	Type of job full time (1) part time (2) unknown (3)		28
	PATIENT'S CONTACT		
25	Patient's phone number		29
26	Name of caregiver 1		30
27	Contact of caregiver 1		31
28	Phone number of caregiver 1		32
29	Relationship between patient and caregiver 1 Spouse (1) Siblings (2) Children (3) Parents (4) Friends (5) Others (6)		33
30	Name of caregiver 2		34
31	Contact of caregiver 2		35
32	Phone number of caregiver 2		36
33	Relationship between patient and caregiver 2 Spouse (1) Siblings (2) Children (3) Parents (4) Friends (5) Others (6)		37
	RISK FACTORS		
34	Who is answering the following questions? Patient (1) Caregiver (2)		38
	Cigarette smoking		

35	Have you ever used tobacco in your life? Yes (1) No (2) *(If yes, move to question 36; if no, move to 49)*		39
36	Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes? Yes (1) No (2) *(If yes, move to question 37; if no, move to 43)*		40
37	Are you daily current smoker? Yes (1) No (2)		41
38	How old were you when you started smoking daily? *(If patient does not remember, ask question 39)*		42
39	How long ago it was? Number of year		43
40	On average, how many of the following do you smoke each day?		
	Manufactory cigarette		44
	Pipes		45
	Cigar		46
41	For those who current do not smoke daily: have you ever smoked daily? Yes (1) No (2) *(If yes, move to 42; if no, move to 45)*		47
42	If yes, how old were you when you started smoking daily? *(If patient cannot remember, ask question 43)*		48
43	Do you remember how long ago it was? Year		49
44	When you smoked, on average, how many of the following do you smoke everyday?		
	Manufactory cigarette		50
	Pipes		51
	Cigar		52
45	How old were you when you stopped smoking daily? *(If patient does not remember, move to question 46)*		53
46	Do you remember how long ago it was? Year		54

47	Do you currently use chewing tobacco? Yes (1) No (2)		55
48	If yes, do you use tobacco chewing daily Yes (1) No (2)		56
	Alcohol		
49	Have you ever consumed an alcoholic drink such as beer, wine, spirits, and fermented cider? Yes (1) No (2) *(If yes, move to 50; if no, move to 55)*		57
50	Have you consumed an alcoholic drink within the past 12 months Yes (1) No (2)		58
51	During the past 12 months, how frequently have you had at least one alcoholic drink? Daily (0) 5-6 days/week (1) 1-4 days/week (2) 1-3 days/month (3) <1time/month (4)		59
52	When you drank alcohol, on average, how many standard alcoholic drinks did you have in one day? (use picture)		60
53	Have you consumed an alcoholic drink within the past 7 days? Yes (1) No (2) Unknown (9)		61
54	Have you consumed an alcoholic drink within the past 30 days? Yes (1) No (2) Unknown (9)		62
	COMORBIDITY		
	High blood pressure		
55	When was the last time your blood pressure was measured by a health worker?		63

	Less than 12 months (1) 1-5 years (2) Not any time during last 5 years (3)		
56	Have you ever been told by a health worker that you have high blood pressure? Yes (1) No (2) Unknown (9)		64
57	In the last 12 months, have you been told by a health worker that you had high blood pressure? Yes (1) No (2) Unknown (9)		65
	Diabetes		
58	In the last 12 months, have you had your blood sugar level measured? Yes (1) No (2) Unknown (9)		66
59	Have you ever been told by a health worker that you have diabetes? Yes (1) No (2) Unknown (9)		67
60	Have you received any treatment for diabetes? Yes (1) No (2) Unknown (9)		68
61	Has the patient ever had a stroke in the past? Yes (1) No (2) Unknown (9)		69
	Current chronic diseases		
62	Heart chronic disease Yes (1) No (2) Unknown (9)		70
63	Chronic lung disease Yes (1) No (2) Unknown (9)		71

64	Chronic kidney disease Yes (1) No (2) Unknown (9)		72
65	Chronic liver disease Yes (1) No (2) Unknown (9)		73
66	Cancer Yes (1) No (2) Unknown (9)		74
67	Weight (kilogram)		75
68	Weight by nurse or staff Yes (1) No (2)		76
69	Is it estimated by nurse of by self-report from patients? Yes (1) No (2)		77
70	Height (m)		78
71	Height by nurse or staff Yes (1) No (2)		79
72	Is it estimated by nurse of by self-report from patients? Yes (1) No (2)		80
	Pre-stroke disability		
73	Before stroke onset, did patient have disability? Yes (1) No (2) Unknown (9)		81
	If yes, give details for the severity and type of disability		82
74	Dominant arm Right (1) Left (2)		83

	Unknown (3)						
75	Which side has weakness now None of all (1) Right (2) Lef (3) Unknown (4)						84
76	Does patient have dementia before stroke? Yes (1) No (2) Unknown (9)						85
77	Before stroke, has patient had a disorder of speaking function such as slurred speech? Yes (1) No (2) Unknown (9)						86
	Estimated costs related to another hospital, before admission to the 115 People's Hospital						
78	Has the patient been admitted to another hospital due to this stroke before he/she is in 115 Hospital? Yes (1) No (2)						87
	In another hospital before 115						
79	Length of stay						88
80	Estimated cost						89
81	Medical cost (invoice)						90
82	Non-medical cost						91
83	Transportation						92
84	Food						93
85	Sundry expenses						94
	Costs related to hospitalisation in the 115 People's Hospital Hospital						
	Non-medical cost at Stroke Unit in 115 People's Hospital						
86		Food for patient	Food for caregiver	Transportation	Paid caregiver	Sundry expense	
	Date 1						
	Date 2						
	Date 3						
	Date 4						
	Date 5						

	Date 6					
	Date 7					
	Total	(95)	(96)	(97)	(98)	(99)

	Indirect cost at 115					
87	Average income/day of patient					100
88	Number of caregivers					101
		Main job	Daily income	Number of day off	Total	
89	Caregiver 1					(102)
90	Caregiver 2					(103)
91	Caregiver 3					(104)
92	Caregiver 4					(105)
93	Caregiver 5					(106)

	If before admitted to 115, if patient stayed in other hospital longer than 1 day, ask indirect costs at that hospital?		
94	Average income of caregiver 1		107
95	Number of day off		108
96	Average income of caregiver 2		109
97	Number of day off		110
98	Average income of caregiver 3		111
99	Number of day off		112
	Source of payment		
100	What are the sources of money did the household get to pay for medical costs and other expenditure related to the stroke? Yes (1) No (2)		
	Saving		113
	Mortgage		114
	Relative support		115
	Sell assets/property		116
	Loan		117
	Insurance		118
	Other (give detail)		119
	Socio-economic status of family		
101	Number of person in the family		120

102	Average income per month of household from salary		121
103	Does the household have another income source (such as renting, interest, personal business etc) Yes (1) No (2) Unknown (9)		122
104	If yes, average income per month of household from other sources		123
105	Expenditure for food for household per month		124
106	Total expenditure per month for household		125
	Wealth index		
107	Do you have which assets as follow Yes (1) No (2)		
	Telephone		126
	Radio		127
	Television		128
	VCD/DVD player		129
	Air conditioner		130
	Fridge		131
	Hot water machine		132
	Computer		133
	Gas cooker		134
	Microwave		135
	Bicycle		136
	Motorbike		137
	Car		138
108	If patient survived hospitalisation, what was the discharge destination o the patient? Home (1) Other hospital/nursing home (2) Rehabilitation (3) Other (give detail)		139
109	If patients return to home, give detail place of their home Ho Chi Minh City (1) Outside Ho Chi Minh City (2)		140

PART 3: NEUROLOGISTS FILL THIS FORM

Name of patient …… Sex: Male/Female Year of birth …….
Hospital ID ……**.....**Admission ID…….

1. Severity of stroke (NIHSS score)					D1
2. Disability level of stroke (Modified Rankin score)					D2
3. Type of stroke IS (1) ICH (2) SAH (3) Undetermined (4)					D3
4. Mechanism/ subtype of ischaemic stroke (TOAST) Embolic in large vessel (1) Cardioembolic (2) Embolic in small vessel (3) Other (4)					D4
	Place an X in the appropriate column				Code
		Yes (1)	**No (2)**	**Unknown (9)**	
5	**Risk factors**				
	Atrial fibrillation				D5
	High blood pressure				D6
	Hyperlipidemia				D7
	Valvular heart disease				D8
	Diabetes				D9
6	**Complication**	Yes (1)	No (2)	Unknown (9)	
	Pneumonia				D10
	Urinary tract infection				D11
	Extracranial bleeding				D12
	Bed sore				D13
	Falls				D14
	Myocardial infraction				D15
	Others				D16
7	At discharge time, what is patient's condition? Stable (1) Very severe (2) Unknown (3)				D17
8	Date of discharge				D18

Appendix 2F: Three-month follow-up questionnaire

A. GENERAL INFORMATION			
1	Patient ID		C1
2	Patient name		C2
3	Admission ID		C3
4	Survey Assistant Code		C4
5	Date of filling questionnaire		C5
6	Landline phone number		C6
7	Mobile number		C7
8	Address		C8
9	Person respondent's full name		C9
10	The respondent person is Patient (1) Spouse (2) Siblings (3) Children (4) Parents (5) Friends (6) Others (7)		C10
11	Who is main caregiver? Spouse (2) Siblings (3) Children (4) Parents (5) Friends (6) Others (7)		C11
B. VITAL STATUS			
12	Was it possible to follow up the patient at three months post stroke? Yes (1)		C12

	No (2) Unknown (9)		
13	What is the vital status at three months post stroke Still alive (1) Deceased (2) Unknown (9)		C13
14	If patient dead at three months, date of death (dd/mm/yyyy)		C14
C. FOR RECURRENT STROKE			
15	In the past 1 month, have you ever had (new) following symptoms?		
	Face muscle weakness Yes (1) No (2) Unknown (9)		C15
	Arm or leg weakness Yes (1) No (2) Unknown (9)		C16
	Slurred speech Yes (1) No (2) Unknown (9)		C17
16	During last month, have you been readmitted to hospital as a consequence of another stroke or for any stroke related problems? Yes (1) No (2) Unknown (9)		C18
17	Is the patient currently at a hospital? Yes (1)		C19

	No (2) Unknown (9)		
18	If yes, please give detail		C20
19	Number of time to re-admit a hospital		C21
	For the first re-admission:		
20	In what hospital (give name of hospital and department)		C22
21	Reason to re-admission		C23
22	How many days in hospital?		C24
23	Total out of pocket expenditure for this re-admission		C25
	For the second re-admission:		
24	In what hospital (give name of hospital and department)		C26
25	Reason to re-admission		C27
26	How many days in hospital?		C28
27	Total out of pocket expenditure for this re-admission		C29
	For the third re-admission:		
28	In what hospital (give name of hospital and department)		C30
29	Reason to re-admission		C31
30	How many days in hospita		C32
31	Total out of pocket expenditure for this re-admission)		C33
D. FOR DIRECT COSTS			
	D1. Medical expenses (doctor, medication, rehabilitation)		
32	Did you use health insurance for health check up Yes (1) No (2)		C34

	Unknown (9)		
33	Total costs related to stroke treatment during last month		C35
34	Source of payment for treatment of stroke (including hospital fees and other stroke-related fees)? Yes (1) No (2)		
	Saving		C36
	Mortgage		C37
	Relative support		C38
	Sell assets/property		C39
	Loan		C40
	Insurance		C41
	Other (give detail)		C41 b
	Doctor consultant fee (total out of pocket money)		
35	Average doctor consult fee per time		C42
36	Number of time for visit doctor during last month (3^{rd} month)		C43
37	Where and how many times has patient meet his/her doctor		C44
	Private consultant room (1)		
	115 hospital with health insurance (2)		
	115 hospital, with no health insurance (3)		
	Other place, give detail		
	Nurse consultant fee		
38	Average nurse consultant fee per time		C45
39	Number of time per month (3rd month)		C46
	Medication		
40	How many prescriptions that doctor have given you during last month (3rd month)?		C47

41	How much have you paid for each prescriptions?		
	Prescription 1		C48
	Prescription 2		C49
	Prescription 3		C50
	Prescription 4		C51
	Traditional /Chinese medicine		C52
	Rehabilitation		
42	Average fee for rehabilitation per time		C53
43	Number of time in last month (3rd month)		C54
44	***Other medical costs***		C55
	D2. Estimated nonmedical expenses		
45	Special dietary		C56
46	Transportation cost from home to hospital/doctor/ rehabilitation		C57
47	Home modification		C58
48	Special equipment and aids		C59
49	Other		C60
E. FOR INDIRECT COSTS: LOSS OF PRODUCTIVITY OF CAREGIVERS			
50	***Caregiver 1***		
	Income per day		C61
	Days of care patients in last month		C62
51	***Caregiver 2***		
	Income per day		C63
	Days for take care patients in last month		C64
52	***Caregiver 3***		
	Income per day		C65
	Days for take care patients in last month		C66
53	***Caregiver 4***		
	Income per day		C67
	Days for take care patients in last month		C68

F. EMPLOYMENT STATUS OF PATIENT			
54	During last month, did patient work? Yes (1) No (2) Unknown (9) *(If say "yes", move to next question; if not, move to question 59)*		C70
55	Details of work		C71
56	Does patient currently work? Yes (1) No (2) Unknown (9)		C72
57	If yes, what was the type of this work full-time (1) part-time (2) Unknown (9)		C73
58	Compare to number of working hours before stroke The same (1) Decreased (2)		C74
G. LIVING ARRANGEMENT			
59	Current residential status Stay alone (1) With family/relative (2) With friends (3) Other (4) Unknown (9)		C75
62	As a consequence of stroke, have you needed to change your place of residence? Yes (1) No (2) Unknown (9)		C76

63	If yes, give reason		C77
64	Number of person in the family now		C78
H. SOCIOECONOMIC STATUS OF FAMILY			
65	Average income per month of household from salary		C79
66	Compared to income prior stroke, current income is: Unchanged (1) Decreased (2) Increased (3) Unknown (9)		C80
67	Does the household have another income (such as renting, interest, personal business, etc) Yes (1) No (2) Unknown (9)		C81
68	If yes, average income per month of household from other sources		C82
69	Expenditure for food for household per last month		C83
70	Total expenditure of last month for household		C84
	Wealth index		
71	In your household now, do you have the following assets Yes (1) No (2)		
	Telephone		C85
	Radio		C86
	Television		C87
	VCD/DVD player		C88
	Air conditioner		C89
	Fridge		C90
	Hot water machine		C91

	Computer		C92
	Gas cooker		C93
	Microwave		C94
	Bicycle		C95
	Motorbike		C96
	Car		C97
72	Source of payment for treatment last three months Yes (1) No (2) Unknown (9)		
I. DISABILITY			
73	Modified Rankin Scale (give one score)		C105
	• No symptoms at all (0) • No significant disability. Able to carry out all usual activities, despite some symptoms (1) • Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities (2) • Moderate disability. Requires some help, but able to walk unassisted (3) • Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted (4) • Severe disability. Requires constant nursing care and attention, bedridden, incontinent (5) • Dead (6)		
74	Who is answering the following questionnaire for quality of life Patient (1) Caregiver (2)		C106

Appendix 2G: Visual show card to estimate alcohol consumption

A small cup (30 ml) of spirit

A glass (120 ml) of wine

A glass of beer (285 ml)

Chapter 3: Hospital-based surveillance of stroke over 12 months at a tertiary teaching hospital in Ho Chi Minh City, Viet Nam

3.1. Preface

In this chapter, the results of hospital-based surveillance of frequency of stroke types, stroke severity and 28-day case-fatality of stroke patients admitted to a tertiary teaching hospital in Ho Chi Minh City during a 12 months period are presented. The incidence density of hospital-admitted first-ever stroke in Ho Chi Minh City is estimated. This surveillance study utilised Step 1 of a standardised method, "STEPwise approach to stroke surveillance", which was developed by the WHO. In subsequent chapters, the author will present the outcomes of a cohort of first-ever stroke patients beyond the hospitalisation. The text in this chapter is under review as an original research manuscript for consideration of publication in the International Journal of Stroke. The appendix of this chapter (Appendix 3) has been prepared as online supplementary data for the manuscript.

3.2. Introduction

Stroke is the second most common cause of death worldwide [308], and a major contributor to morbidity and disability [308,309]. There is some evidence [2] that LMICs are now experiencing greater incidence of stroke than HICs. Reductions in communicable diseases have resulted in greater longevity [64,65] and increased numbers of people surviving to the ages at which stroke is more common. In Viet Nam, the percentage of the population aged greater than 60 years (the ageing index in the context of a LMIC) has risen from 24.3% in 1999 to 35.5% in 2009, and is still rising [66]. Concurrently, the cardiovascular risk factor profile of the population has worsened with reductions in physical activity and increases in intake of fat, salt and sugar [310] and smoking [311]. It is therefore likely that stroke is becoming more common in Viet Nam, but there have been only two studies of stroke in the country [107,108] and one of those was conducted over 20 years ago [108].

To remedy this critical lack of information, we conducted 12 months of surveillance of stroke at a tertiary teaching hospital in Ho Chi Minh City, Viet Nam's largest city. Our aim was to determine the frequency of stroke types, stroke severity and 28-day case-fatality. A secondary aim was to estimate the incidence of hospital-admitted first-ever stroke in Ho Chi Minh City.

3.3. Methods

Subjects

The study was conducted at 115 People's Hospital, one of three hospitals in Ho Chi Minh City with a specialist stroke facility. During the 12-month period from 9 December 2009 to 8 December 2010, we monitored admissions to the Emergency Department, Intensive Care Unit, Cardiology Department and Stroke Unit. A pilot study had confirmed that these departments captured almost all stroke patients with most treated in the Stroke Unit (70 beds with 14 physicians) [295]. Stroke was confirmed by stroke neurologists using the standard clinical definition of sudden onset of focal neurological symptoms of presumed vascular origin [3]. All patients received brain imaging (computed tomography or magnetic resonance

imaging) to exclude other causes and define stroke type. The exclusion criteria were transient ischemic attack, defined as focal neurologic symptoms lasting less than 24 hours, or discharge within 24 hours from the hospital.

Stroke patients may be transferred to 115 People's Hospital from other provinces to receive specialist care. Accordingly, only 61.5% (3,084/5,017) of the 5,017 patients registered in this study provided an address in Ho Chi Minh City as their residential location, with the remainder drawn from surrounding provinces.

Data collection

This study used Step 1 (events in hospital) of STEPS-Stroke methodology [98]. Data collection instruments were developed in consultation with local clinicians, and translated into Vietnamese and back-translated to check accuracy. Each department recorded patient details and dates of transfer between departments. A treating physician recorded stroke types, signs and symptoms at onset, risk factors (atrial fibrillation, smoking status, diabetes, hyperlipidaemia, hypertension and valvular heart disease), and assessed severity on the modified Rankin Scale (mRS) [122]. Nurses contacted patients or their caregivers by telephone at 28 days post-stroke to assess case-fatality.

Geospatial analysis

For 2,921 of the 3,083 stroke patients, residential addresses were geocoded to Ho Chi Minh City wards for which population data were sourced from the General Statistics Office. Age- and sex-specific population data for each ward in Ho Chi Minh City were provided by the General Statistics Office of Viet Nam (Statistical Office in Ho Chi Minh City, 2012). Crude stroke hospital-admitted incidence rates for each ward were calculated by dividing the total number of patients traced to each ward by the aggregate population of the ward. To produce **Figure 3.1**, these crude rates were smoothed by firstly taking a weighted average of the number of strokes among residents of each ward and of all surrounding wards, and secondly of the population of each ward and of all surrounding wards, and then dividing the smoothed number of strokes in each ward by its smoothed population. The weights used varied inversely with the distance (d) between the centres of wards. The particular weights used to produce Figure 1 were calculated as 1/(d+1). The smoothed rates were ranked and arbitrary cut-points (selected by the software used) were used to produce the coloured zones of Figure 3.1. Zone 1 is the area closest to the hospital. Zone 2 encloses Zone 1 and extends to areas further from the hospital. Zone 3 encloses Zone 2 and extends to areas even further from the hospital.

Data analysis

Analysis of variance and chi-squared analysis was used to compare means and proportions respectively. Associations of severity of stroke with study factors (age, sex and stroke type) were analysed by log multinominal regression [312]. Risk and relative risk of case-fatality to 28 days was estimated by Poisson regression with robust standard errors [313]. Hospital-admitted stroke incidence density were age-standardised to the new World Standard Population [314] using the direct method. Details are provided in the Appendix 3.

Ethics

All participants and their carers provided written consent. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee and the ethics committee of 115 People's Hospital in Viet Nam.

3.4. Results

During the 12 month study period, 5,017 (54.3% male, 75.6% first-ever stroke) patients with stroke were registered (**Table 3.1**).

Table 3.1: Characteristics of stroke patients admitted to 115 People's Hospital in Ho Chi Minh City, Viet Nam, during the 12 month period December 2009 to December 2010.

	Men (N=2,722)	Women (N=2,295)
Characteristic	% (n)	% (n)
Age group		
< 45 years	8.2 (224)	5.1 (118)
45-54 years	23.8 (648)	13.6 (312)
55-64 years	26.6 (724)	20.4 (468)
65-74 years	21.7 (591)	25.2 (578)
75-84 years	16.3 (444)	28.1 (646)
85+ years	3.3 (91)	7.5 (173)
Type of stroke *		
Ischaemic stroke	74.3 (2,013)	81.8 (1,856)
ICH	24.3 (659)	16.6 (379)
SAH	0.4 (11)	0.9 (21)
Undetermined	1.0 (26)	1.7 (31)
Stroke onset		
First-ever stroke	74.9 (2,031)	75.5 (1,729)
Recurrent stroke	24.6 (668)	23.8 (544)
Undetermined	0.5 (14)	0.7 (18)
Functional status on admission †		
mRS=0	1.2 (32)	1.2 (28)
mRS=1	8.5 (230)	7.5 (172)
mRS=2	13.8 (375)	12.6 (290)
mRS=3	27.6 (750)	23.1 (531)
mRS=4	35.4 (961)	38.6 (886)
mRS=5	13.3 (362)	16.8 (385)
mRS=6	0.3 (7)	0.1 (3)
Unknown	0.2 (5)	0 (0)
Vital status at 28 days		
Alive	73.1 (1,989)	71.2 (1,634)
Deceased	9.7 (265)	10.4 (239)
Unknown	17.2 (468)	18.4 (422)

* IS = ischaemic stroke, ICH = intra-cerebral haemorrhage, SAH = subarachnoid haemorrhage.

† Disability assessed by the modified Rankin Scale (mRS) administered during hospital stay.

Mean ages were 61.8 (SD 13.1) years for men and 67.5 (SD 13.2) years for women, with more males (58.6%) than females (39.1%) aged < 65 years at onset. Relatively more women had severe disability (mRS=4/5) on admission (p<0.001) even after adjustment for age. Among patients with confirmed vital status, case-fatality at 28 days was 12.2% (males 11.8%, females 12.8%), with another 18% of patients having unknown vital status due to loss to follow-up. Patients lost to follow-up were similar to those followed up (Table **A3.4** in the Appendix 3).Mean age of occurrence differed by stroke type (p<0.001): 65.5 (SD 13.2) years for ischaemic stroke (IS), 60.4 (SD 13.6) years for ICH (p<0.001), and 62.4 (SD 15.5) years for subarachnoid haemorrhage (SAH). Female patients were older than male patients at onset of IS (p <0.001) and ICH (p <0.001). Summary data on symptoms, signs and vascular risk factors of stroke are shown in **Table A3.2** and **Table A3.3** in the Appendix 3.In this study, 77.5% (3,875/5,002) had moderate-to-severe disability (mRS=3/4/5) (**Table 3.2**).

Table 3.2: Severity of disability classified by sex, age group and history of stroke.

		Least severe (mRS=0/1)*	Intermediate (mRS=2/3)*	More severe (mRS=4/5)*
	N	% (n)	% (n)	% (n)
First-ever stroke				
Men	2,023	9.6 (194)	43.2 (874)	47.2 (955)
< 45 years	202	13.9 (28)	41.6 (84)	44.5 (90)
45-54 years	534	9.9 (53)	45.1 (241)	44.9 (240)
55-64 years	526	11.0 (58)	42.2 (222)	46.8 (246)
65-74 years	401	8.5 (34)	44.9 (180)	46.6 (187)
75-84 years	305	5.6 (17)	42.6 (130)	51.8 (158)
85 years+	55	7.3 (4)	30.9 (17)	61.8 (34)
Women	1,726	9.3 (161)	35.9 (619)	54.8 (946)
< 45 years	100	15.0 (15)	36.0 (36)	48.0 (48)
45-54 years	252	10.7 (27)	40.1 (101)	49.2 (124)
55-64 years	351	8.8 (31)	42.2 (148)	49.0 (172)
65-74 years	430	10.0 (43)	34.0 (146)	56.0 (241)
75-84 years	471	7.9 (37)	33.3 (157)	58.8 (277)
85 years+	122	6.6 (8)	25.4 (31)	68.0 (83)
Recurrent stroke				
Men	666	9.8 (65)	37.1 (247)	53.2 (354)
< 45 years	20	15.0 (3)	40.0 (8)	45.0 (9)
45-54 years	107	13.1 (14)	43.0 (46)	43.9 (47)
55-64 years	190	12.1 (23)	39.0 (74)	49.0 (93)
65-74 years	181	7.2 (13)	36.5 (66)	56.4 (102)
75-84 years	133	7.5 (10)	31.6 (42)	60.9 (81)
85 years+	35	5.7 (2)	31.4 (11)	62.9 (22)
Women	544	7.0 (38)	35.9 (195)	57.2 (311)
< 45 years	18	16.7 (3)	38.9 (7)	44.4 (8)
45-54 years	57	8.8 (5)	43.9 (25)	47.4 (27)
55-64 years	115	7.0 (8)	36.5 (42)	56.5 (65)
65-74 years	141	9.9 (14)	38.3 (54)	51.8 (73)
75-84 years	165	4.2 (7)	35.2 (58)	60.6 (100)
85 years+	48	2.1 (1)	18.8 (9)	79.2 (38)

* mRS = disability assessed on the modified Rankin Scale.

From **Table 3.2**, the risk of more severe disability (mRS=4/5) increased with age (men p<0.001, women p<0.001) similarly for men and women (interaction of age group with sex, p=0.368) and for recurrent and first-ever strokes (interaction of age group with recurrence, p=0.218) but in a more pronounced manner for IS than for ICH (interaction p<0.001, **Table A3.5**, Appendix 3).

Table 3.3: Estimated incidence of hospital-admitted stroke at 115 People's Hospital among residents of Ho Chi Minh City during the 12 month period December 2009 to December 2010.

					Age-standardised
Sex	Zone*	Cases	Pop	Rate (95% CI) †	Rate (95% CI) ‡
Men	1(a)	43	48,302	89.0 (62.4-115.6)	103.0 (70.1-135.9)
	1(b)	110	100,867	109.1 (88.7-129.4)	124.1 (99.7-148.5)
	1	117	124,166	94.2 (77.2-111.3)	109.2 (88.5-130.0)
	1,2	309	411,287	75.1 (66.8-83.5)	91.4 (80.8-102.0)
	1,2,3	524	784,623	66.8 (61.1-72.5)	85.0 (77.4-92.7)
	All	1,182	3,450,515	34.3 (32.3-36.2)	56.6 (53.2-60.1)
Women	1(a)	59	55,952	105.4 (78.5-132.4)	101.6 (74.8-128.4)
	1(b)	119	118,596	100.3 (82.3-118.4)	91.1 (74.3-108.0)
	1	134	146,777	91.3 (75.8-106.8)	82.3 (68.0-96.6)
	1,2	293	473,789	61.8 (54.8-68.9)	58.9 (52.0-65.7)
	1,2,3	500	895,498	55.8 (50.9-60.7)	56.5 (51.5-61.6)
	All	1,038	3,760,092	27.6 (25.9-29.3)	36.7 (34.4-39.0)
Persons	1(a)	102	104,254	97.8 (78.9-116.8)	104.8 (83.7-126.0)
	1(b)	229	219,463	104.3 (90.8-117.9)	105.6 (91.5-119.7)
	1	251	270,943	92.6 (81.2-104.1)	94.2 (82.2-106.2)
	1,2	602	885,076	68.0 (62.6-73.5)	72.7 (66.7-78.6)
	1,2,3	1,024	1,680,121	60.9 (57.2-64.7)	68.9 (64.5-73.2)
	All	2,220	7,210,607	30.8 (29.5-32.1)	45.4 (43.5-47.4)

* Zone 1(a)=all wards within Zone 1 with centres located ≤1 kilometre from the hospital. Zone 1(b)=all wards within Zone 1 with centres located ≤12 kilometres from the hospital. Zone 1=area closest to the hospital. Zone 2=area surrounding Zone 1. Zone 3=geographically-dispersed area.

† Rate per 100,000 (95% confidence interval).

‡ Rate per 100,000 age-standardised to the new world standard population

Patients with ICH had greater risk of more severe disability (men p<0.001, women p<0.001) than those with IS (**Table A3.5**, Appendix 3). First-ever events were relatively more common among patients with ICH (adjusted for age, males p<0.001, females p<0.001) than among patients with IS (**Table A3.5**, Appendix 3). Those with ICH had greater 28 day case-fatality (adjusted for age and stroke recurrence, men p<0.001, women p<0.001) that was not fully accounted for by the higher proportions with first-ever stroke (adjusted for age and stroke recurrence, p<0.001).The characteristics of stroke patients who were Ho Chi Minh City residents are shown in **Table A3.1** (Appendix 3).

The annual incidence density of hospital-admitted stroke among those living closest to 115 People's Hospital (Zone 1) was as high as 109.1 per 100,000 population for males and 105.4 per 100,000 for females. Age standardised to the new world standard population, the values

were 124.1 (95% confidence interval 99.7, 148.5) per 100,000 for males and 101.6 (95% confidence interval 74.8, 128.4) per 100,000 for females. Hospital admissions for stroke were greatest in regions closer to the hospital (Zone 1, red color), and declined with greater distance from the hospital (see **Figure 3.1**).

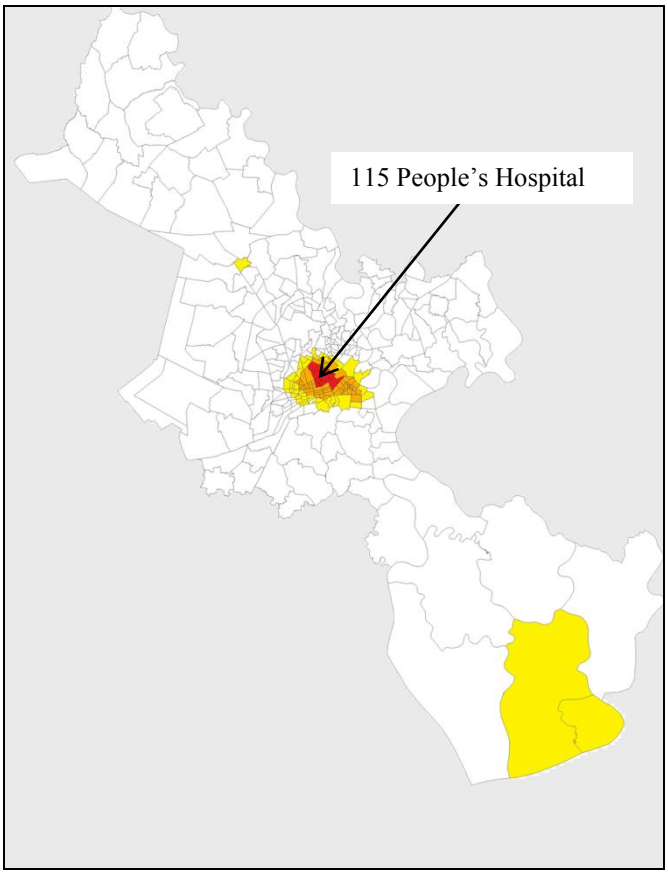


Figure 3.1: Areas with high proportions of residents admitted to 115 People's Hospital with a diagnosis of stroke during the study period.
The figure illustrates Zone 1 (red colour), Zone 2 (orange colour) and Zone 3 (yellow colour).

3.5. Discussion

Our principal findings from 12 months of surveillance of stroke in a major teaching hospital in Ho Chi Minh City, Viet Nam, are that incidence density was lower than that in other LMICs but mean age at diagnosis and stroke type distribution were similar. Female patients were on average older than male patients at the time of stroke, a large proportion of patients had severe deficits, and 28 day case-fatality was lower than expected.

The only previous estimate of stroke incidence in Viet Nam was 142 per 100,000 from a community-based study [108] conducted during 1994-95 in three provinces of southern Viet Nam, including Ho Chi Minh City. Based on those data, Feigin et al. [2] projected that the incidence of stroke in Viet Nam in 2010 would have been 254.78 per 100,000 person-year. Our lower estimate may be explained by under-ascertainment and urban-rural differences. Hospital-based studies are estimated to miss 14% of cases in Australia [106], and possibly as

much as 50% of cases in Viet Nam [315]. In addition, rates may be higher in rural areas where 70% of the population lives. Le et al. [108] provided estimates of incidence for each of two rural provinces and for Ho Chi Minh City. The rural rates were 2.0 and 2.7 times higher than their estimate for Ho Chi Minh City.

The young age of onset of stroke in our study (64.4 years) is consistent with the average age of 64.2 years from hospital-based STEPS-Stroke surveys in five LMICs (India, Iran, Mozambique, Nigeria and Russia) [27], and around 5 to 6 years lower than in HICs [2], with important social and economic implications in these countries.

Similar to the finding of the five LMICs review [27], females patients were generally older than male patients at the time of stroke. Approximately 40% of the age difference was attributable to differences in the age structure of the male and female populations of Ho Chi Minh City, with 60% left to be accounted for by differences in vascular risk factors and biological differences such as the protective effects of endogenous oestrogen for pre-menopausal women [25]. Whilst we did not find differences in risk of stroke between self-reported smokers and non-smokers in our patient group, or for self-reported alcohol intake, smoking and alcohol intake are likely candidates because around half of the adult Vietnamese male population are current smokers compared with 2.1% of women [73], and excessive alcohol intake is reported by 22.3% of men but by only 1.4% of women [73].

Using the mRS as a marker of stroke severity, over 75% had moderate-to-severe deficits (mRS $\geq$ 3). This is greater than estimates of 38.5% from hospital-based studies in Mumbai [12] and 57.5% in Trivandrum [28]. One possible explanation is that 115 People's Hospital received a disproportionate number of severe strokes referred from other hospitals. The 28-day case-fatality (12.2%) among patients with known vital status was less than that (36.4%) of the only other Vietnamese study [107], which was conducted in the rural province of Da Nang, and smaller too than estimates for other LMICs [12,113]. Ours is likely to be an underestimate due to under-ascertainment of severe cases. The cultural beliefs in Viet Nam that favour palliation at home, with early discharge of patients with a poor prognosis, have been documented by Tirschwell et al. [107]. In addition, almost 20% of patients were lost to follow-up. Our estimated case-fatality would be higher if a disproportionately large number of these patients had died.

The clinical presentations of the patients were typical with limb weakness, face weakness and slurred speech the most common signs and symptoms. These align with findings in HICs [77] and suggest that campaigns of the type used in HICs to raise awareness of the early signs and symptoms of stroke can be considered for adoption in Viet Nam.

This study has several strengths. It was conducted in accordance with WHO protocols in a tertiary teaching hospital with a specialist stroke unit using modern imaging technology following a pilot study [295] to standardise diagnostic criteria. While most cases came from the stroke unit, other departments provided notification of potential cases ensuring hospital-wide surveillance. Finally, by geocoding patient addresses, we were able to map an approximate catchment area of the hospital to provide an estimate of the incidence of hospital-admitted stroke.

Nevertheless, our study has some limitations. There is no exclusive catchment area for the hospital because local residents can attend any other hospital, including one with a stroke unit that is close to 115 People's Hospital. Possible under-ascertainment of cases at the extremes of severity cannot be discounted because patients with mild strokes may not attend hospital,

and more severe cases may be discharged or die early. Together with failure to recontact nearly 20% of patients, this means that our assessments of incidence and 28-day case-fatality are probably underestimates.

3.6. Conclusions

In a tertiary hospital in urban Viet Nam, strokes occurred at an earlier age and resulted in more severe disability than is usual in HICs and some LMICs. These findings suggest that the burden of stroke in Viet Nam is substantial.

3.7. Postscript

Reported in this chapter were the findings of 12-month hospital-based surveillance study of stroke in Viet Nam including mean age of patients at stroke onset, frequency of stroke types, stroke severity 28-day case-fatality of patients with stroke admitted to a major teaching hospital in Ho Chi Minh City during 12 months. Estimates of the incidence of hospital-admitted first-ever stroke in Ho Chi Minh City were also presented in this chapter. It was found that although the incidence density and 28-day case-fatality were lower than expected possibly due to under-ascertainment and Vietnamese cultural beliefs that favor palliation at home, the mean age at diagnosis and stroke type distribution were similar to other findings from LMICs. In particular, a large proportion of patients had severe deficits suggesting more severe stroke. Additional information on methods and results related to this surveillance study are reported in Appendix 3. In the next chapter, case-fatality and severity of functional outcomes of survivors at three months after stroke from a cohort study of patients with first-ever stroke will be presented.

Appendix 3: Additional information on methods and findings derived from the 12-month hospital-based surveillance study

Results

Mean age at stroke onset

Restricting the analyses to the 3,083 stroke patients from Ho Chi Minh City allowed us to examine whether differences in the age distributions of the male and female populations of Ho Chi Minh City accounted for the younger mean age of male patients (**Table A3.1**).

Table A3.1: Characteristics Ho Chi Minh City residents with a diagnosis of stroke admitted to 115 People's Hospital, Viet Nam, during the period 9 December 2009 to 9 December 2010.

	Men (N=1645)	Women (N=1434)
	% n/N	% n/N
Age group		
<45 years	8.9 (147)	5.2 (75)
45-54 years	23.7 (390)	12.0 (172)
55-64 years	26.3 (433)	19.3 (277)
65-74 years	22.2 (365)	23.6 (339)
75-84 years	15.5 (255)	30.9 (445)
85+ years	3.4 (55)	9.0 (130)
Confirmation of stroke		
Neuroimaging diagnosis	100.0 (1,645)	100.0 (1,438)
Type of stroke [*]		
Ischaemic stroke	73.1 (1,198)	79.6 (1,141)
ICH	25.1 (412)	18.0 (258)
SAH	0.6 (10)	1.1 (16/)
Undetermined	1.2 (20)	1.3 (19)
Stroke onset[†]		
First-ever stroke	73.9 (1,212)	73.6 (1,056)
Recurrent stroke	25.5 (419)	25.6 (365)
Undetermined	0.6 (10)	0.8 (12)
Vital status at 28 days[‡]		
Alive	75.5 (1,212)	72.7 (1,011)
Deceased	11.4 (184)	12.6 (175)
Unknown	13.1 (210)	14.7 (205)

[*] Type of stroke: 5 cases with missing data, ICH = intra-cerebral haemorrhagic stroke, SAH = subarachnoid haemorrhagic stroke.; [†] 4 cases with missing data.; [‡] 86 cases with missing data.

In 2010, the female population was markedly older (there were greater number of females than males in each successively higher-ordered five-year age group commencing with the 45-49 years group). Standardised to the female population of Ho Chi Minh City, the mean age of male stroke patients was 64.1 (SD 13.4) years. Our sample included 1934 patients (1,077

males, 857 females) who provided a residential address outside of Ho Chi Minh City (**Table A3.1)**.

Compared with their city counterparts, they were more likely to have had an ischaemic stroke [80.4% vs 77.1% (2,339/3,035), p=0.006] and a first-ever stroke [77.8% (1492/1918) vs 74.3% (2,268/3,054), p=0.005]. They also appeared to have lesser 28-day mortality [9.4% vs 13.9%, p=0.001] and greater loss to follow-up [20.1% (389/1934) vs 16.3% (501/3083), p<0.001].

Signs and symptoms of stroke at admission time

Signs and symptoms of stroke were similar for males and females (**Table A3.2**). More than half the patients experienced slurred speech. Limb weakness was present for about 90% of patients while face weakness was present for about 70%.

Table A3.2: Symptoms and signs of stroke among patients with stroke admitted to 115 People's Hospital in Ho Chi Minh City, Viet Nam.

	Males (N=2,718)	Females (N=2,295)
	% (n)*	% (n)*
Symptoms		
Dizziness	28.7 (781)	26.5 (607)
Headache	37.6 (1,021)	32.1 (737)
Blurred vision	5.5 (150)	4.2 (97)
Double vision	1.6 (43)	1.9 (43)
Slurred speech	55.5 (1,507)	57.1 (1,309)
Difficulty swallowing	15.3 (417)	17.6 (404)
Confusion	17.0 (462)	21.9 (503)
Seizure	2.5 (67)	2.5 (58)
Signs		
Consciousness	17.2 (468)	22.0 (506)
Brain stem sign	6.6 (178)	5.8 (133)
Limb weakness	90.8 (2,465)	90.3 (2,069)
Face weakness	72.3 (1,964)	69.2 (1,585)
Loss of sensation	35.5 (964)	33.8 (775)
Visual deficit	2.6 (71)	2.8 (65)
Neglect	5.2 (140)	5.1 (118)
Aphasia/dysphasia	19.8 (538)	21.8 (500)
Apraxia	9.4 (256)	10.5 (240)
Ataxic gait	2.9 (79)	2.6 (60)

* The percentages of patients with symptoms and signs do not sum to 100 because some patients reported more than one symptom or sign.

Vascular risk factors among patients

Table A3.3 shows the prevalence of vascular risk factors among the stroke patients. More than three-quarters of males and females had hyperlipidaemia, and nearly 90 per cent had

hypertension. Atrial fibrillation, diabetes and valvular heart disease were more common among female patients than male patients, and smoking was more common among the men.

Table A3.3: Vascular risk factors among patients with stroke admitted to 115 People's Hospital in Ho Chi Minh City, Viet Nam.

	Males (N=2,674)		Females (N=2,223)	
Vascular risk factors	(%)	(n)	%	(n)
Atrial fibrillation	4.5	(119)	9.3	(206)
Current smoking	30.6	(819)	1.2	(26)
Diabetes	13.0	(348)	21.1	(469)
Hyperlipidemia	75.1	(2,009)	77.1	(1,714)
Hypertension	89.6	(2,398)	88.9	(1,976)
Valvular heart disease	4.9	(130)	9.8	(217)

Comparison with other studies

Relative to the summary data for males from the review of STEPS-Stroke surveys at nine sites in five low and middle income countries (India, Iran, Mozambique, Nigeria and Russia),[27] relatively more of the distribution of male Vietnamese patients fell in lower age categories ($p<0.001$) (**Table A3.4**). The distributions also differed for females ($p<0.001$) but not in the same systematic way: greater proportion of the Vietnamese distribution fell in the lowest and highest age categories. Had the relative frequencies of the three stroke types in this study matched those of the 5-country review, the median age of diagnosis for females in this study would have been 69.1 (95% confidence interval 68.1, 70.1) years.

Distribution of type of stroke classified by sex, age group and stroke onset

Among persons with ischaemic stroke, the trend of reduced proportions with first-ever stroke with increasing age was more pronounced for males than females ($p<0.001$, **Table A3.5**) and overall the proportion with first-ever stroke was greater for females than for males ($p=0.024$). Otherwise the trends were not statistically distinguishable by sex, and there were no differences by sex in the age-adjusted proportions with first-ever stroke (ICH $p=0.286$). First-ever events were relatively more common among patients with ICH (adjusted for age, males $p<0.001$, females $p<0.001$) than among patients with IS.

Comparison characteristics of patients who lost not follow up with those who were followed up at 28 days post stroke

Table A3.6 shows characteristics of patients who were lost to follow up and those who were followed up at 28 days post stroke. Patients who were not followed up [mean age 65.5 (SD 13.5) years] were older than those who were followed up [mean age 64.2 (SD 13.6) years]. Compares to patients who were followed up, those who were lost to follow up were less likely to be Ho Chi Minh City residents. There were no differences in sex, type of stroke, recurrent stroke and severity of disability.

Table A3.4: Comparison age of stroke onset in our study with that of other STEPS Stroke studies.

	This study		STEPS stroke review study [27]	
	Male (N=2,722)	Female (N=2,295)	Male (N=2,981)	Female (N=2,484)
Age: median (IQR)	61 (52-72)	70 (58-78)	65 (54-73)	69 (58-76)
Age group				
<45 years	8.0% (224)	5.1% (118)	11.0% (335)	9.0% 214
45-54 years	24.0% (648)	13.6% (312)	16.0% (465)	11.0% 261
55-64 years	27.0% (724)	20.4% (468)	22.0% (659)	18.0% 448
65-74 years	22.0% (591)	25.2% (578)	28.0% (847)	32.0% 789
75-84 years	16.0% (444)	28.2% (646)	19.0% (572)	25.0% 614
85+ years	3.0% (91)	7.5% (173)	3.0% (103)	9.0% 158

Table A3.5. Proportions of first-ever stroke, severe disability and 28-day survival status classified by sex, age group and type of stroke

	First-ever stroke	Severe disability (mRS=4/5)	28-day survival
	% n/N	% n/N	% n/N
All stroke	75.6 (3760/4972)*	51.9 (2594/5002)	87.8 (3623/4124)
Ischaemic	73.7 (2828/3837)†	46.6 (1802/5002)	92.0 (2928/3182)
Male	72.8 (1456/1999)	42.2 (848/2008)	92.8 (1539/1659)
< 45 years	89.4 (126/141)	33.8 (48/142)	96.6 (112/116)
45-54 years	80.9 (330/408)	33.8 (138/408)	93.6 (322/344)
55-64 years	71.2 (385/541)	39.7 (216/544)	94.7 (431/455)
65-74 years	67.2 (315/469)	46.2 (217/470)	90.4 (349/386)
75-84 years	70.8 (259/366)	50.4 (186/369)	91.6 (274/299)
85 years+	55.4 (41/74)	57.3 (43/75)	86.4 (51/59)
Female	74.7 (1372/1838)	51.4 (954/1856)	
< 45 years	81.9 (68/83)	42.2 (35/83)	94.2 (65/69)
45-54 years	79.7 (181/227)	39.9 (91/228)	95.8 (183/191)
55-64 years	73.4 (276/376)	44.6 (168/377)	96.3 (308/320)
65-74 years	75.2 (357/475)	51.2 (247/482)	90.9 (360/396)
75-84 years	72.8 (390/536)	57.8 (314/543)	88.7 (386/435)
85 years+	70.9 (100/141)	69.2 (99/143)	77.7 (87/112)
Haemorrhagic	81.2 (932/1148)‡	69.6 (792/1138)	73.5 (695/945)
Male	82.1 (575/700)	67.7 (475/702)	75.6 (450/595)
< 45 years	93.4 (71/76)	67.5 (52/77)	77.9 (53/68)
45-54 years	89.4 (203/227)	65.9 (147/223)	77.5 (155/200)
55-64 years	82.4 (136/165)	75.3 (125/166)	72.6 (106/146)
65-74 years	76.7 (79/103)	67.6 (71/105)	78.4 (58/74)
75-84 years	66.7 (44/66)	79.7 (55/69)	69.5 (41/59)
85 years+	93.3 (14/15)	86.7 (13/15)	61.5 (8/13)
Female	82.1 (357/435)	72.7 (317/436)	70.0 (245/350)
< 45 years	89.7 (26/29)	65.5 (19/29)	81.8 (18/22)
45-54 years	86.3 (63/73)	74.3 (55/74)	71.9 (41/57)
55-64 years	83.8 (67/80)	82.3 (65/79)	64.6 (42/65)
65-74 years	83.3 (65/78)	82.1 (64/78)	76.2 (45/59)
75-84 years	82.4 (75/91)	69.6 (64/92)	63.6 (49/77)
85 years+	80.0 (20/25)	87.5 (21/24)	47.8 (11/23)

* 45 cases with missing data on first-ever stroke,
† 32 cases with missing data on stroke onset among patients with ischaemic stroke,
‡ 13 cases with missing data on stroke onset among patients with haemorrhagic stroke.

Table A3.6. Characteristics of patients who were lost to follow up and those who were followed up at 28 days

	Lost to follow up (N=890)	Followed-up (N=4127)
	% (n)	% (n)
Sex		
Male	47.4 (422)	45.4 (1873)
Age group		
< 45 years	6.5 (58)	6.9 (284)
45-54 years	17.2 (153)	19.6 (807)
55-64 years	21.1 (188)	24.3 (1004)
65-74 years	25.6 (228)	22.8 (941)
75-84 years	23.7 (211)	879 (21.3)
85+ years	5.8 (52)	5.1 (212)
Residence		
Ho Chi Minh City residence	56.3 (501)	62.6 (2582)
Type of stroke*		
Ischaemic stroke	77.8 (687)	77.4 (3182)
ICH	19.8 (175)	21.0 (863)
SAH	0.7 (6)	0.6 (26)
Undetermined	1.7 (15)	1.0 (42)
Stroke onset†		
First-ever stroke	75.4 (667)	75.1 (3093)
Recurrent stroke	24.3 (215)	24.2 (997)
Undetermined	0.3 (3)	0.7 (29)
Severity of stroke‡		
Least severe	8.6 (76)	9.4 386)
Intermediate	39.5 (351)	38.8 (1595)
Most severe	51.9 (461)	51.9 (2133)

* Type of stroke: missing data of type of stroke for 7 lost follow-up cases and 14 followed up cases, ICH = intra-cerebral haemorrhage, SAH = subarachnoid haemorrhage

† 5 lost follow up cases and 8 followed up with missing data

‡ 2 lost follow up cases and 13 followed up with missing data

Chapter 4: Case-fatality and functional status three months after first-ever stroke in Viet Nam

4.1. Preface

The previous chapter provided information on the occurrence and clinical manifestation of stroke in Viet Nam from a hospital-based surveillance study during 12 months. To investigate further outcomes of stroke after patients are discharged from the hospital, a cohort study of 450 patients with first-ever stroke was conducted by the author. This chapter reports the case-fatality and functional outcomes at three months. At the time of this thesis submission, the text in this chapter had been prepared as a a manuscript for submission in consideration of publication in the European Journal of Neurology. The appendix to this Chapter (Appendix 4) has been prepared as online supplementary data of the manuscript.

4.2. Introduction

In 2010, stroke was the second most common cause of death and the third most common cause of disability-adjusted life-years (DALYs) worldwide [2]. Reduced functional status (disability) is common among survivors, with approximately 30%-40% of patients having reduced function three months after stroke [159].

These observations have come largely from HICs [2]. However, there is growing recognition that incidence and prevalence of stroke are increasing in LMICs although data describing the burden in such regions are limited [61]. The age-standardised incidence of stroke in LMICs is up to 23% greater than in HICs [2]. Moreover, stroke among patients aged < 75 years in LMICs is more than 3-fold that in HICs [2], translating to a greater burden at younger ages.

Viet Nam is a LMIC in south east Asia that is undergoing rapid epidemiological transition. Currently, information on the occurrence and burden of stroke in Viet Nam is scarce. Given this critical lack of information, we followed a cohort of first-ever stroke patients admitted to a stroke unit in a tertiary teaching hospital to three months after stroke onset. The aim was to assess case-fatality and functional outcomes at three months after stroke, and thereby to provide critical information for planning the health system response to the growing burden of stroke in Viet Nam.

4.3. Methods

Subjects

Patients in this cohort study were recruited from the stroke unit of 115 People's Hospital, a major teaching hospital in Ho Chi Minh City, Viet Nam. The study inclusion criteria were first-ever ischaemic stroke (IS) or intracerebral haemorrhage (ICH) confirmed by a neurologist, age≥ 16 years, living in Ho Chi Minh City, with occurrence in the last 7 days and acute stroke treatment completed within the stroke unit. Forty-seven patients died and 27 were lost to follow-up, resulting in 376 patients who completed the follow-up interview at three months (**Figure 4.1**).

Data collection

At baseline, clinical states including type of stroke, severity of impairment on the National Institute Health Stroke Scale (NIHSS) [115], and severity of functional status (disability) on the modified Rankin Scale (mRS) [122], were assessed by a neurologist in the stroke unit. Patients or their main caregivers were interviewed by research assistants to collect data on sociodemographic and economic status, lifestyle and clinical risk factors, and health status before stroke (disability and co-morbidity). Patients were contacted by telephone at one month and two months after stroke onset to collect data on vital status. If the patient had died during follow up, date of death and cause of death were recorded from information provided by caregivers. Three months after stroke onset, patients or their proxies were interviewed in their homes by research assistants to assess severity of disability on the mRS.

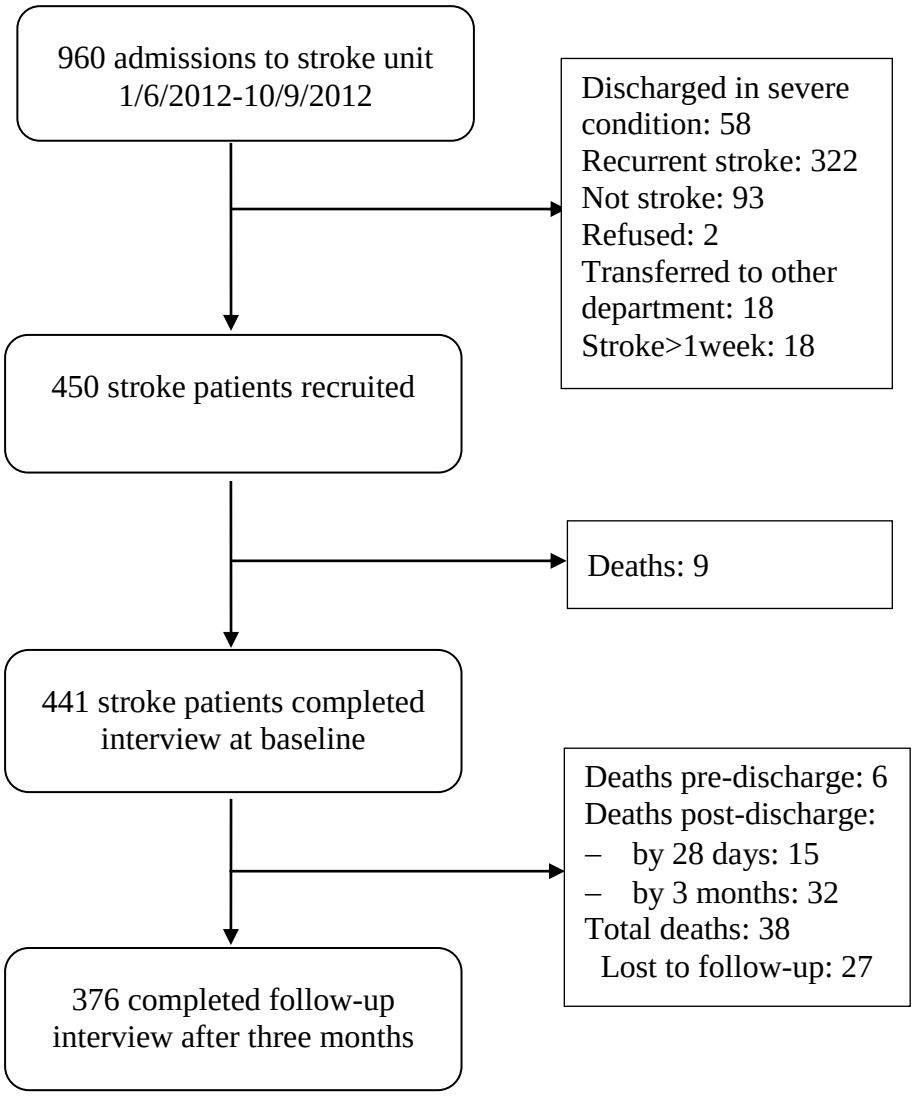


Figure 4.1: Flowchart for demonstration of participant recruitment and follow up to three months.

Data analysis

Student's t-tests and chi-squared tests were used to test differences between means and proportions respectively. Log multinomial regression [312] was used to estimate risk and relative risk (RR) of mRS disability category at the three-month follow-up. Results are presented for four optimal groupings of mRS scores: *least severe* (mRS=0/1), *intermediate* (mRS=2/3), *more severe* (mRS=4/5), and *dead* (mRS=6). Patients in the intermediate category (mRS=2/3) had an intermediate pattern of risk, and were excluded from estimation (as one category must be). It was not possible to estimate a single odds ratio or relative risk for these ordered data because none of the logit-link [316] or log-link [317] ordinal regression models could be fitted without statistically significant ($p<0.003$) loss of model fit. Risk and relative risk of change in mRS category was estimated by conditioning on baseline mRS category (the mRS score at three months then represents change in mRS category). For comparison with published data, linear regression methods were used to estimate mean change in mRS scores (calculated as mRS at three months *less* mRS at hospital) with positive mean values indicating worsening of functional status on average. Tests of trend of categorical factors with more than two attributes were undertaken by replacing binary covariates with a single ordinal covariate. Statistical interaction was assessed by testing the coefficient of the covariate formed as the product of covariates for the study factor and the potential modifier, or by multivariate tests of multiple product terms. The fit of each final model was carefully assessed, and covariates were rescaled where necessary to improve fit. All statistical tests were two-sided with a 5% allowance for type I error.

Modified Rankin Scale (mRS)								
No symptom (mRS=0)	No disability (mRS=1)	Slight disability (mRS=2)	Moderate disability (mRS=3)	Mod. severe disability (mRS=4)	Severe disability (mRS=5)	Dead (mRS=6)	Levels	Information retained $\boldsymbol{\beta' V^{-1} \beta}$ (%)
0	1	2	3	4	5	6	7	367.3 (100%)
0 + 1		2	3	4	5	6	6	364.9 (99%)
0 + 1		2 + 3		4	5	6	5	359.7 (98%)
0 + 1		2 + 3		4 + 5		6	4	351.1 (96%)
0 + 1 + 2 + 3				4 + 5		6	3	320.6 (87%)
0 + 1 + 2 + 3				4 + 5 + 6			2	230.0 (63%)

Figure 4.2: Amalgamation of adjacent categories of the modified Rankin Scale (mRS) scores. The amalgamation shown at each step is that which retained the maximum information from the ordinal log-link regression of the mRS categories on covariates for age and sex.

Figure 4.2 shows that for a forwards-descending continuation ratio log-link ordinal model [317] with age and sex as covariates, amalgamating categories of the mRS as we have done

resulted in almost no loss of information (96% of information is retained). The index of precision used for this assessment was the multivariate Wald statistic $\hat{\boldsymbol{\beta}}'\hat{\mathbf{V}}^{-1}\hat{\boldsymbol{\beta}}$, where $\hat{\boldsymbol{\beta}}$ is the vector of estimated coefficients and $\hat{\mathbf{V}}$ is the estimated covariance matrix of $\hat{\boldsymbol{\beta}}$. Figure 2 also shows that any further amalgamation of categories would result in more substantial loss of information, and that the optimal binary classification for our data is at mRS=4 with the two groupings of mRS<4 and mRS≥ 4.

4.4. Results

From June to September 2012, 450 consecutive first-ever stroke patients were ascertained as being eligible for the study.

Table 4.1: Characteristics of a cohort of patients with first-ever stroke in Ho Chi Minh City, Viet Nam, on discharge from hospital. *

	Men (N=230)	Women (N=211)
Age		
Mean age (SD)	59.6 (12.8)	65.6 (14.5)
Median age (IQR)	58.5 (50-69)	68.0 (55-77)
< 45 years	11.7% (27)	7.1% (15)
45-54 years	26.5% (61)	17.5% (37)
55-64 years	26.5% (61)	21.8% (46)
65-74 years	21.7% (50)	19.0% (40)
75+ years	13.5% (31)	34.6% (73)
Comorbidity		
None	73.9% (170)	67.3% (142)
1	18.3% (42)	23.7% (50)
2-6	7.8% (18)	9.0% (19)
Pre-stroke disability †		
Yes	4.8% (11)	9.5% (20)
No	95.2% (219)	90.5% (191)
Type of stroke		
Ischaemic stroke	73.0% (168)	79.6% (168)
ICH	27.0% (62)	20.4% (43)
Severity of impairment (NIHSS)§		
Mean score (SD)	7.6 (5.4)	8.8 (6.1)
Severe (NIHSS > 7)	41.3% (92)	48.0% (96)
Not severe (NIHSS ≤ 7)	58.7% (131)	52.0% (104)
Functional status (mRS)§		
Mean score (SD)	3.1 (1.1)	3.2 (1.1)
Median score (IQR)	3.0 (3-4)	4.0 (3-4)
mRS = 1	11.0% (25)	11.1% (23)
mRS = 2	13.6% (31)	13.0% (27)
mRS = 3	28.5% (65)	23.7% (49)
mRS = 4	43.9% (100)	46.4% (96)
mRS = 5	3.1% (7)	5.8% (12)

*. This information is provided for the 441 patients alive at discharge.
† Patient self-report.
§ Assessed during initial hospital stay.

Of these, 9 patients (7 men and 2 women) died prior to enrolment. Fifty two percent (230/441) of the remaining 441 patient participants were men (Table 1). The median age was 67 (interquartile range IQR 52-74) years. Ischemic stroke (IS) accounted for 76.2% (75/108) of the cases and was slightly more common among women than men. Severity of impairment during initial hospital stay, assessed by mean NIHSS score, was 8.2 (SD 5.8). The median NIHSS score was 6.0 (IQR 4-12). Women had greater severity of impairment than men at admission (p=0.04). The mean mRS of functional status at admission was 3.2 (SD 1.1) while the median score was 3.2 (IQR 3-4) There were only minor differences by sex in these clinical characteristics (**Table 4.1**).

Socio-demographic information, tobacco smoking, alcohol consumption and comorbidities are summarised in Appendix 4 (**Table A4.1).** Whilst tobacco smoking and alcohol consumption were rare among women patients, three quarters of the men had smoked at any time (34.5 years average duration and 25.5 average pack-years of smoking), and one-half had consumed alcohol during the past 30 days.

Table 4.2: Outcomes of stroke at three months.

	Men	Women
	% (n/N)	% (n/N)
Mortality		
In-hospital case fatality	4.2 (10/237)	2.3 (5/213)
28-day case fatality	6.3 (15/237)	7.0 (15/213)
3 month case fatality	9.3 (22/237)	11.7 (25/213)
Functional status (mRS) at three months		
Mean score (SD)	2.1 (1.4)	2.7 (1.4)
Median score (IQR)	2.0 (1-4)	3.0 (2-4)
mRS=0	11.3 (23/204)	3.5 (6)
mRS=1	29.9 (61/204)	21.5 (37/172)
mRS=2	23.5 (48/204)	23.3 (40/172)
mRS=3	12.3 (25/204)	18.6 (32/172)
mRS=4	20.1 (41/204)	22.1 (38/172)
mRS=5	2.9 (6/204)	11.1 (19/172)

The outcomes of the 450 eligible subjects are summarised in **Table 4.2.** In-hospital case fatality was 3.3% (15/450), 28-day case fatality was 6.7% (30/450), and three-month case fatality was 10.4% (47/450). If one half of the 58 early discharges were first-ever cases and all had died, and if deaths occurred among the other non-participating (2) or lost (27) patients as it did for the remaining study participants, case-fatality would have been 9.1% in hospital, 12.7% at 28 days and 16.4% at three months.

Among the 376 survivors who completed the assessment of disability at three months follow-up (**Table 4.2**), the average mRS was 2.7 (SD 1.7), while the median mRS was 2.0 (IQR 1-4). The average mRS score of female patients who were followed up was 28% (95% CI 14.4%, 41.7%) greater (p<0.001) than the average mRS score of their generally younger male counterparts, and 18% (95% CI 5.1%, 31.4%) greater (p=0.007) adjusted for age.

Table 4.3: Risk and relative risk of disability, and of death, at three months following first-ever stroke in Ho Chi Minh City, Viet Nam.

		Least severe (mRS=0/1)		Intermediate (mRS=2/3)	Most severe (mRS=4/5)		Death (mRS = 6)	
	N	% (n)	RR (95%CI) †	% (n)	% (n)	RR (95%CI) †	% (n)	RR (95%CI) †
Age group								
< 45 years	40	50.0 (20)	1.00	37.5 (15)	5.0 (2)	1.00	7.5 (3)	1.00
45–54 years	95	44.2 (42)	0.88 (0.61,1.27)	36.8 (35)	15.8 (15)	3.17 (0.76,13.2)	3.2 (3)	0.42 (0.09,2.00)
55–64 years	101	36.6 (37)	0.76 (0.51,1.12)	42.6 (43)	16.8 (17)	3.32 (0.80,13.7)	4.0 (4)	0.52 (0.12,2.23)
65–74 years	82	18.3 (15)	0.37 (0.21,0.64)***	31.7 (26)	41.5 (34)	8.25 (2.09,32.6)**	8.5 (7)	1.13 (0.31,4.15)
75+ years	96	13.5 (13)	0.31 (0.17,0.56)***	27.1 (26)	37.5 (36)	7.07 (1.78,28.2)**	21.9 (21)	2.77 (0.86,8.96)
Trend			0.75 (0.68,0.84)***			1.41 (1.23,1.61)***		1.60 (1.23,2.10)**
Sex								
Male	219	38.4 (84)	1.00	33.3 (73)	21.5 (47)	1.00	6.8 (15)	1.00
Female	195	22.1 (43)	0.68 (0.51,0.92)*	36.9 (72)	29.2 (57)	1.10 (0.8,1.52)	11.8 (23)	1.19 (0.65,2.18)
Co-morbidities								
None	291	35.7 (104)	1.00	33.7 (98)	23.7 (69)	1.00	6.9 (20)	1.00
1	89	21.3 (19)	0.71 (0.47,1.06)	36.0 (32)	29.2 (26)	1.02 (0.71,1.45)	13.5 (12)	1.94 (1.05,3.61)
2–6	34	11.8 (4)	0.40 (0.16,1.01)	44.1 (15)	26.5 (9)	0.91 (0.52,1.61)	17.6 (6)	2.00 (0.92,4.36)
Trend			0.68 (0.51,0.93)*			0.98 (0.78,1.22)		1.43 (1.03,2.00)*
Pre-disability								
No	384	32.0 (123)		36.2 (139)	23.7 (91)	1.00	8.1 (31)	1.00
Yes	30	13.3 (4)	0.74 (0.29,1.88)	26.0 (6)	43.3 (13)	1.24 (0.80,1.91)	23.3 (7)	1.70 (0.86, 3.35)
Type of stroke								
IS	313	31.9 (100)	1.00	34.8 (109)	24.3 (76)	1.00	8.9 (28)	1.00
ICH	101	26.7 (27)	0.67 (0.48,0.92)*	35.6 (36)	27.7 (28)	1.42 (1.03,1.96)*	9.9 (10)	1.36 (0.73,2.52)
Impairment §¶								
Not severe	221	47.1 (104)	1.00	36.7 (81)	13.6 (30)	1.00	2.7 (6)	1.00
Severe	178	11.2 (20)	0.29 (0.19,0.45)***	33.7 (60)	38.8 (69)	2.35 (1.58,3.49)***	16.3 (29)	4.29 (1.77,10.4)***
Disability §¶#								
Least severe	46	58.7% (27)	1.00	41.3 (19)	0.0 (0)	1.00	0.0 (0)	1.00
Intermediate	156	43.8% (71)		34.6 (56)	19.1 (31)		2.5 (4)	
More severe	201	14.4% (29)	0.40 (0.25,0.52)***	33.8 (68)	35.8 (72)	1.98 (1.35,2.90)***	15.9 (32)	6.03 (2.14, 17.0)**

* denotes p<0.05; ** denotes p<0.01; *** denotes p<0.001;

† RR(95%CI) = relative risk (95% confidence interval), adjusted for age and sex, but estimates for age adjusted for sex only and estimates for sex adjusted for age only;

§ During initial hospital visit; ¶ NIHSS >7 (severe) compared with NIHSS≤7 (not severe); # Least severe (mRS = 0/1), Intermediate (mRS=2/3), More severe (mRS=4/5).

With the mRS scores (including death) at three months collapsed optimally to four groupings (see Methods), risk of least disability (mRS=0/1) was markedly lower for older patients and women (**Table 4.3**) and, adjusted for age and sex, for those with more comorbidities or ICH.

Risk of most severe disability (mRS=4/5) were elevated among older patients and those with ICH. Risk of having died was greater for older patients and those with co-morbidity or pre-stroke disability. The increased risks of most severe disability (RR 1.36, 95% CI 0.98, 1.80) and of death (RR 1.72, 95% CI 0.93, 3.20) for women were substantially reduced by adjustment for age.

Association of these outcomes with education, tobacco smoking, socio-demographic factors, alcohol consumption and clinical factors were inconsistent and none was statistically significant (see **Table A4.2**, Appendix 4).

Table 4.4 shows the estimates of relative risk additionally adjusted for severity of disability at admission. When conditioned on baseline severity in this way, the estimates represent relative risks of attaining (changing to) each mRS category during the 3 month period.

The factors predictive of attaining each category during the three months (**Table 4.4**) were the same factors that were associated with elevated risk of each category at three months (**Table 4.3**), and the relative risk estimates for factors other than pre-disability and baseline impairment were generally similar. In regression analyses of change in the mRS scores between baseline and three months (mRS at three months *less* mRS at baseline) conducted to allow comparison of results with published data, the same predictors of change were identified (see **Table A4.4**).

On average, functional status improved by 0.5 points (SD 1.6). The greatest improvements were experienced by patients less than 65 years of age for whom the average sex-adjusted improvement was 1.1 (95% confidence interval 0.9, 1.3) points, and particularly those younger than 45 years for whom the average improvement was 1.5 (95% CI 1.1, 2.0) points. There were statistically significant but smaller differences between subjects classified by sex (adjusted for age) and number of co-morbidities and pre-stroke disability (adjusted for age and sex).

Among patients who had assessment of functional status at baseline and at three months (**Figure 4.3**), 50.0% (204/409) had improved over the three months with recovery relatively less common [17.4% (8/46)] among those with no significant disability (mRS=1) at admission, 23.5% (96/409) had the same functional status, and 26.7% (100/409) had deteriorated with 15.2% (28/181) of those with moderately severe disability (mRS=4) and 23.5% (4/17) of those with severe disability (mRS=5) at baseline having died during follow-up.

Table 4.4: Risk and relative risk of disability, and of death, at three months following first-ever stroke in Ho Chi Minh City, Viet Nam, with conditioning on disability at baseline.

		Least severe (mRS = 0/1)		Intermediate (mRS = 2/3)	Most severe (mRS=4/5)		Death (mRS = 6)	
	N	%(n)	RR(95%CI) †	%(n)	%(n)	RR(95%CI) †	%(n)	RR(95%CI) †
Age group								
< 45 years	40	50.0(20)	1.00	37.5(15)	5.0(2)	1.00	7.5(3)	1.00
45–54 years	95	44.2(42)	0.65(0.50,0.85)**	36.8(35)	15.8(15)	3.77(0.92,15.45)	3.2(3)	0.75(0.16,3.46)
55–64 years	101	36.6(37)	0.62(0.47,0.83)**	42.6(43)	16.8(17)	3.50(0.86,14.21)	4.0(4)	0.90(0.25,3.25)
65–74 years	82	18.3(15)	0.40(0.25,0.64)***	31.7(26)	41.5(34)	7.85(2.03,30.40)**	8.5(7)	1.13(0.31,4.15)
75+ years	96	13.5(13)	0.34(0.20,0.58)***	27.1(26)	37.5(36)	6.16(1.58,24.0)**	21.9(21)	2.48(0.86,7.60)
Trend			0.78(0.70,0.86)***			1.32(1.16,1.51)***		1.45(1.11,1.89)**
Sex								
Male	219	38.4(84)	1.00	33.3(73)	21.5(47)	1.00	6.8(15)	1.00
Female	195	22.1(43)	0.69(0.53,0.90)**	36.9(72)	29.2(57)	1.20(0.89,1.61)	11.8(23)	1.04(0.59,1.84)
Co-morbidities								
None	291	35.7(104)	1.00	33.7(98)	23.7(69)	1.00	6.9(20)	1.00
1	89	21.3(19)	0.76(0.52,1.17)	36.0(32)	29.2(26)	0.99(0.71,1.39)	13.5(12)	1.54(0.90,2.65)
2–6	34	11.8(4)	0.43(0.17,1.05)	44.1(15)	26.5(9)	0.89(0.51,1.54)	17.6(6)	3.32(1.25,8.82)
Trend			0.71(0.53,0.95)*			0.96(0.76,1.20)		1.69(1.03,2.00)*
Pre-disability								
No	384	32.0(123)		36.2(139)	23.7(91)	1.00	8.1(31)	1.00
Yes	30	13.3(4)	0.73(0.30, 1.77)	20.0(6)	43.3(13)	1.03 (0.67,1.60)	23.3(7)	8.24(2.19,31.02)
Type of stroke								
IS	313	31.9(100)	1.00	34.8(109)	24.3(76)	1.00	8.9(28)	1.00
ICH	101	26.7(27)	0.88(0.63,1.22)*	35.6(36)	27.7(28)	1.36 (0.98,1.87)	9.9(10)	0.76(0.39,1.50)
Impairment §¶								
Not severe	221	47.1(104)	1.00	36.7(81)	13.6(30)	1.00	2.7(6)	1.00
Severe	178	11.2(20)	0.40(0.25,0.66)***	33.7(60)	38.8(69)	1.86 (1.19,2.91)**	16.3(29)	1.68(0.61,4.60)

* denotes p<0.05, ** denotes p<0.01, *** denotes p<0.001,

† RR(95%CI) = relative risk (95% confidence interval), adjusted for age, sex and mRS category at admission, but estimates for age adjusted for sex and mRS category only, and estimates for sex adjusted for age and modified Rankin Scale category only, ‡ No test of trend is provided because no a priori ranking order exists. A likelihood ratio test of the three binary covariates yielded p=0.83

§ During initial hospital visit, ¶ NIHSS >7 (severe) compared with NIHSS≤7 (not severe).

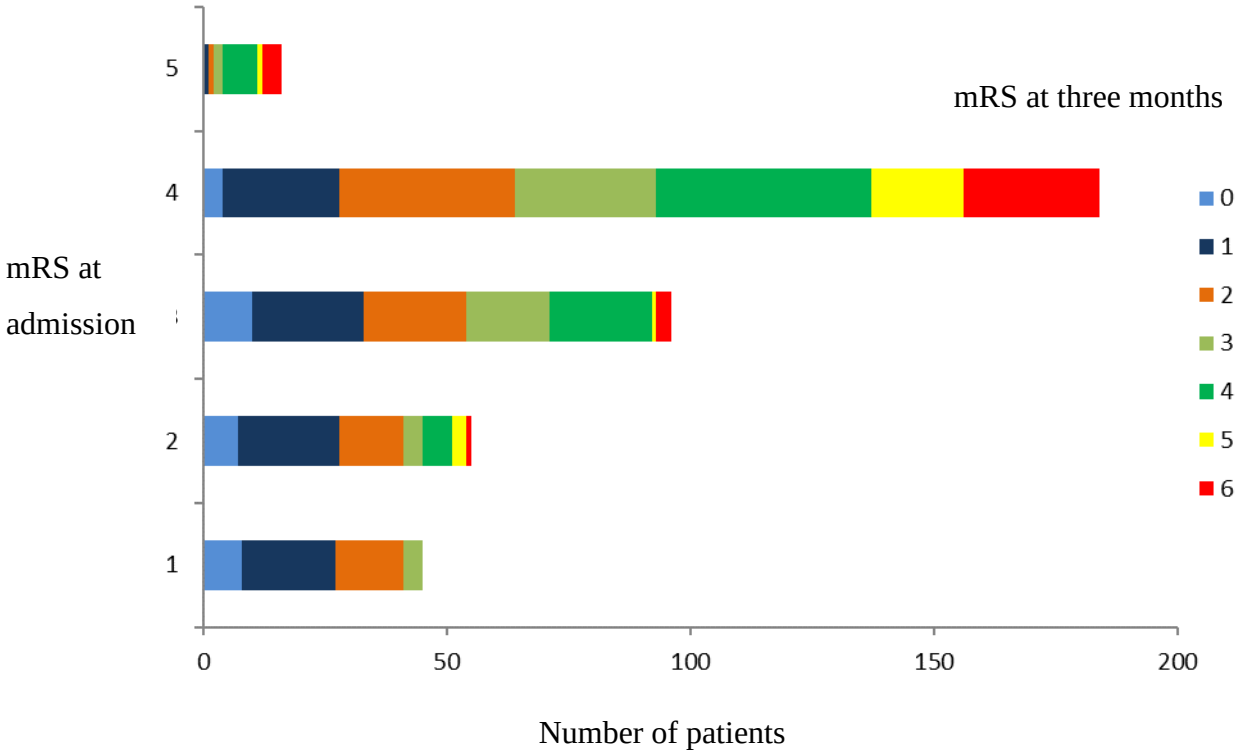


Figure 4.3: Distribution of disability assessed by mRS at admission and at 3 month post stroke.

4.5. Discussion

In this cohort of consecutive first-ever stroke patients admitted to the stroke unit of a major teaching hospital in Ho Chi Minh City, one-third of survivors had no significant disability (mRS=0/1) after three months, another one-third had slight or moderate disability (mRS=2/3), and the remaining one-third had most severe disability (mRS=4/5) or were dead. During the three months following stroke onset, one-half of surviving patients had reduced severity of disability, one quarter had remained unchanged, and the remaining one-quarter had worsened or had died.

In relation to the distribution of functional status at three months assessed using the mRS, cut-points mRS=1 [130,131] of mRS=2 [318] have been previously used to distinguish favourable outcomes from unfavourable outcomes among surviving patients. The dichotomy at cut-point 3 distinguishes independence from dependence in activities of daily living. In our study, 38.9 % had mRS $\geq$ 3 and a further 9.2% of our cohort had died. The proportion of survivors with dependent outcomes (mRS $\geq$ 3) in our study (38.9%) was around the mid-point of the range (21-70%) of the proportion of survivors with dependent outcomes in the multicentre study in Western and Central Europe [319]. The proportion with dependent outcomes among survivors with IS was 37.4% in this study, higher than findings for survivors with IS in China (28.0%) [320] and South Korea (29.7%) [303].

In this study, however, the distribution of severity of disability of survivors at three months more naturally fell into three groups: a group with least severity disability (mRS=0/1), an intermediate group with slight or moderate disability (mRS=2/3) and a group with moderately severe or severe disability (mRS=4/5). Less severe disability was more common among younger patients (predominantly men) with IS whereas those with more severe disability tended to be compromised older persons with severe impairment or disability at admission. Greater age [159], increased severity of stroke and greater comorbidity [160] have previously been found to be predictors of poor outcomes at three months, but the identification of a group of young men with IS at the least severe end of the spectrum of disability at three months has not been made previously. In contrast to previous studies [321], we found no evidence for an association between mRS and pre-stroke tobacco smoking, alcohol consumption [161,164] or lower socioeconomic status [165].

The case-fatality in our study may be under-estimated due to under-ascertainment of cases with very severe stroke who either did not present to hospital or were discharged at the request of the family from the emergency department prior to admission to the stroke unit or from the stroke unit prior to registration for this study. The cultural beliefs in Viet Nam that would prompt patients with a poor prognosis to not present to hospital or to seek early discharge, in order to have the end of their lives at home among family members, have been documented by others [107]. Under conservative assumptions about their mortality outcomes, our case-fatality estimates would be higher (12.5% for 28-day mortality and 16.0% for three-month mortality). They would then be more similar to the findings of our previous hospital-based surveillance [322] (12.2% among patients with known vital status at 28 days post-stroke), to estimates of 28-day case fatality in LMICs ranging from 16.0% in Qatar [112] to 34.0% in Malaysia [114], and to estimates of three-month mortality in European multicentre studies ranging from 12.6% to 35.9% in Heuschmann et al. (2010) [159] and from 17.4% to 55.9% in Wolfe et al. [319].

In relation to recovery, half of the patients in this study had improved functional status at three-months. The greatest improvements were experienced by younger patients, particularly among those less than 45 years of age for whom the average improvement was 1.5 points. Huybrechts et al. [323] reported that a shift of 1 point in mRS score at three months post-stroke predicts long-term functional independence and mortality. In this study, patients without comorbidities or disability before stroke had statistically significant improvements in functional status that were less than 1 point on the mRS scale. These findings are consistent with those of other studies in respect of age [324], co-morbidities [325], and pre-stroke disability [159].

Interestingly, women were 36% more likely to have severe disability at three months and 72% more likely to have died than men, but most of this elevation was due to their older age (mean age 65.6 years for women versus 59.6 years for men). When adjusted for age, the increases in risk were reduced to 10% for severe disability and 19% for death. The average recovery in functional status of women was significantly less than that of men when assessed as age-adjusted change over three months in mRS, but the difference was less than one point. These findings are generally consistent with those of several other studies that have reported poorer outcomes for women in terms of survival and functional status [167,245].

This study has several strengths. Firstly, the stroke patients were a consecutive series of patients from a specialist stroke unit with comprehensive clinical assessments made by stroke neurologists at admission and with complete imaging for confirmation of diagnosis. Secondly, there was follow-up of these patients over three months for clinical outcomes and with

functional status at three months assessed by well-trained research assistants who were general medical practitioners in Ho Chi Minh City. Thirdly, our low proportion of loss to follow-up (6.1% at three months compared to 23.4-29.8% for studies in HICs [159,160]) reduces concerns about bias. All data collection was standardised and well-controlled, limiting measurement error as far as possible and with minimal item non-response. Lastly, functional status was assessed on the mRS both at admission and follow-up, and analyses were conducted without unnecessary data reduction in the categories of functional status.

However, our study has some limitations. At baseline, it is likely that we failed to fully ascertain cases at each end of the severity spectrum. Under-ascertainment of severe cases would explain our relatively low case fatality. Information on lifestyle risk factors and on co-morbidities and pre-stroke disability were collected by self-report, and could be subject to random error or bias. Another limitation is the reliance on reports by caregivers of deaths among patients. This information may not be accurate, but more reliable sources of data were not available.

4.6. Conclusion

Case-fatality in this study was low, possibly due to cultural preferences for end-of-life care at home that may prevent severe cases of stroke of being admitted to the stroke unit. The dependency burden was relatively high, however, and this provides evidence of significant pressure on the healthcare system and society.

4.7. Postscript

Reported in this chapter was an investigation of case-fatality and functional outcomes at three months following stroke of a cohort of patients with first-ever stroke admitted to a Stroke Unit in a major teaching hospital in Ho Chi Minh City, Viet Nam. The next chapter will present findings on economic aspects of the burden of stroke on patients, their families, the healthcare system and society.

Appendix 4: Additional reports on functional outcomes at three months after stroke

Characteristics of patients

Table A4.1 summarises socio-demographic characteristics of the participants and information on their pre-stroke comorbidity, tobacco smoking and alcohol consumption

Table A4.1: Characteristics of a cohort of patients with first-ever stroke in Ho Chi Minh City, Viet Nam.*

Characteristic	Men (N=230)	Women (N=211)
Ethnicity †		
Vietnamese	91.7% (211)	91.5% (193)
Chinese	8.2% (19)	8.6% (18)
BMI †		
Mean (SD)	22.8 (3.2)	22.9 (4.0)
Underweight (BMI < 18.5%)	9.6% (22)	12.8% (27)
Normal (18.5% ≤ BMI <23.0%)	42.6% (98)	38.9% (82)
Overweight (23.0% ≤ BMI < 27.5%)	39.6% (91)	37.0% (78)
Obese (BMI≥ 27.5%)	8.2% (19)	10.9% (23)
Marital status †		
Married	89.1% (205)	55.9% (118)
Single	5.2% (12)	6.2% (13)
Divorced	2.2% (5)	1.9% (4)
Widowhood (widower/widow)	3.5% (8)	36.0% (76)
Highest education level †		
No schooling	11.2% (24)	43.5% (83/191)
Primary school	24.3% (52)	31.9% (61)
Secondary school	25.2% (54)	15.7% (30)
High school	24.8% (53)	6.8% (13)
College/university	14.5% (31)	2.1% (4)
Working status †		
Manual work	24.6% (56)	5.7% (12)
Office work	19.7% (45)	16.6% (35)
Home duties/retired	55.7% (127)	77.7% (164)
Wealth index †		
1st quarter (richest)	25.9% (58)	23.0% (48)
2nd quarter	23.2% (52)	21.5% (45)
3rd quarter	27.7% (62)	23.9% (50)
4th quarter (poorest)	23.2% (52)	31.6% (66)
Living with spouse †		
Yes	76.8% (173)	37.0% (76)
No – living with children	17.5% (177)	55.8% (177)
No – living with others	5.7% (20)	7.2% (19)
Tobacco smoking †		
Never smoker	24.3% (56)	94.8% (200)

Characteristic	Men (N=230)	Women (N=211)
Former smoker	20.9% (48)	2.4% (5)
Year smoked: mean(SD)	32.6 (12.7)	33.4 (18.2)
Cigarettes/day: mean(SD)	16.1 (13.1)	14.4 (20.1)
Pack-years: mean(SD)	28.2 (2.2)	19.3 (27.1)
Current smoker	54.8% (126)	2.8% (6)
Year smoked: mean(SD)	34.7 (12.0)	48.2 (15.8)
Cigarettes/day: mean(SD)	13.2 (8.8)	14.4 (7.1)
Pack-years: mean(SD)	24.2 (19.7)	36.3 (21.6)
Alcohol consumption †		
Not last 12 months	29.1% (67)	99.5% (210)
Not last 30 days	21.7% (50)	0.0% (0)
Not last 7 days	16.1% (37)	0.0% (0)
Last 7 days	33.0% (76)	0.5% (1)
Last 12 months	70.9% (163)	99.5% (1)
Days/month: mean (SD)	10.4 (10.5)	30 (n.a.)
Drinks/occasion: mean (SD) ‡	4.9 (4.6)	6.0 (n.a.)
High blood pressure †		
No	48.3% (111)	33.6% (71)
Yes, untreated	12.6% (29)	7.6% (16)
Yes, treated	39.1% (90)	58.8% (124)
Diabetes †		
No	87.4% (201)	84.4% (178)
Yes, untreated	2.2% (5)	1.4% (3)
Yes, treated	10.4% (24)	14.2% (30)
Dementia †		
No	98.7% (14)	93.4% (197)
Yes	1.3% (3)	6.6% (14)
Heart disease †		
No	86.9% (206)	79.2% (167)
Yes	10.4% (14)	20.8% (44)
Lung disease †		
No	95.2% (220)	98.1% (207)
Yes	4.8% (11)	1.9% (4)
Kidney disease †		
No	95.7% (220)	94.8% (200)
Yes	4.8% (11)	1.9% (4)
Liver disease †		
No	95.7% (220)	94.8% (200)
Yes	4.3% (10)	5.2% (11)
Cancer †		
No	96.5% (222)	99.0% (209)
Yes	3.5% (8)	1.0% (2)
Pre-stroke disability †		
Yes	4.8% (11)	9.5% (20)
No	95.2% (219)	90.5% (191)

* The cohort consists of 450 patients, 9 of whom died in-hospital prior to commencement of follow-up. This information is provided for the 441 patients alive at discharge.

† Patient self-report.

‡ Number of standard drinks consumed on a typical drinking occasion.

Greater proportions of women than men were widowed and living with children. Around three times as many male patients as female patients had progressed beyond grade 5 of education. Three quarters of the women were involved in home duties only. Hypertension was self-reported by 48.5% (214/441) of participants, diabetes mellitus by 12.2% (54/441), dementia prior to stroke by 3.9% (17/441) and disability prior to stroke by 7.0% (31/441). Greater proportions of women than men were treated for hypertension, and there were slightly greater proportions of women treated for diabetes, dementia, or disability prior to stroke (**Table A4.1**).

Risk and relative risk of functional status and of death at three months after stroke onset

There were not significant elevations in estimated risk of least severe disability (mRS=0/1), most severe disability (mRS=4/5) or death (mRS=6) – the optimal groupings of mRS scores – for subjects classified by education level, tobacco smoking or pre-stroke disability (Table S2). However, the risk of least disability tended to be greatest and risk of death tended to be least among patients with more education, non-smokers, and those without pre-disability. The associations between mRS groupings and other socio-demographic factors (working status, living arrangements and household wealth), alcohol consumption and clinical factors (high blood pressure, dementia, delayed admission and individual comorbidities) were inconsistent and not statistically significant (**Table A4.2**).

Change in functional status over the three months of follow-up

Table A4.3 shows the estimates of relative risk additionally adjusted for severity of disability at admission. The factors predictive of attaining each category during the three months (**Table A4. 3**) were the same factors that were associated with elevated risk of each category at three months (**Table A4.2**), and the relative risk estimates were generally similar.

On average, functional status improved by 0.5 (SD 1.6) points. **Table A4.4** shows that the recovery was progressively lesser for older patients (adjusted for sex), smaller for women (adjusted for age), and least for those with pre-stroke disability and those with greater numbers of comorbidities (adjusted for sex and age). There were no significant associations between the change of severity of disability over three months of stroke first-stroke onset and other socio-demographic factors (education, working status, and wealth index), tobacco smoking, alcohol consumption and other health status prior stroke (**Table A4.4**).

Table A4.2: Risk and relative risk of disability at three months following onset of first-ever stroke, and of death following first-ever stroke, in Ho Chi Minh City, Viet Nam.

		Least severe (mRS=0/1)		Intermediate (mRS=2/3)	Most severe (mRS=4/5)		Death (mRS = 6)	
	N	%(n)	RR(95%CI) *	%(n)	%(n)	RR(95%CI) *	%(n)	RR(95%CI) *
Weight status								
Underweight	47	21.3(10)	1.00	31.9(15)	27.7(13)	1.00	19.1(9)	1.00
Normal	170	30.6(52)	1.19(0.69,2.03)	32.9(56)	26.5(45)	1.14(0.70,1.85)	10.0(17)	0.70(0.35,1.40)
Overweight	157	34.4(54)	1.29(0.75,2.23)	37.6(59)	21.7(34)	0.95(0.56,1.62)	6.4(10)	0.60(0.26,1.37)
Obese	39	25.6(10)	1.10(0.54,2.26)	38.5(15)	30.8(12)	1.27(0.68,2.33)	5.1(2)	0.40(0.10,2.14)
Trend			1.05(0.89,1.23)			1.02(0.84,1.23)		0.77(0.54,1.09)
Education								
No schooling	134	17.9(24)	1.00	34.3(46)	30.6(41)	1.00	17.2(23)	1.00
Primary school	104	29.8(31)	1.21(0.76,1.94)	39.4(41)	24.0(25)	1.07(0.72,1.60)	6.7(7)	0.50(0.21,1.19)
Secondary school	79	39.2(31)	1.41(0.89,2.24)	32.9(26)	22.8(18)	1.27(0.75,2.17)	5.1(4)	0.51(0.16,1.60)
High school	63	39.7(25)	1.30(0.79, 2.12)	34.9(22)	20.6(13)	1.24(0.68, 2.78)	4.8(3)	0.51(0.13, 1.96)
College/ university	34	47.1(16)	1.96(1.21, 3.19)*	29.4(10)	20.6(7)	0.85(0.41, 1.75)	2.9(1)	0.26(0, 1.96)
Trend			1.13(1.02, 1.27)*			1.00(0.87, 1.15)		0.74(0.53, 1.05)
Working status								
Manual work	70	47.1(33)	1.00	37.1(26)	12.9(9)	1.00	2.9(2)	1.00
Office work	74	47.3(35)	1.14(0.81,1.62)	35.1(26)	13.5(10)	1.01(0.44,2.31)	4.1(3)	1.22(0.21,7.09)
At home/retired	268	21.6(58)	0.84(0.55,1.28)	34.3(92)	31.7(85)	1.17(0.52,2.63)	12.3(33)	2.27(0.41,12.7)
Living with spouse								
Yes	240	36.7(88)	1.00	37.1(89)	21.3(51)	1.00	5.0(12)	1.00
No, with children	146	20.5(30)	1.13(0.78,1.65)	30.1(44)	33.6(49)	0.87(0.60,1.25)	15.8(23)	1.82(0.81,4.08)
No, with others	24	33.3(8)	0.91(0.54,1.56)	41.7(10)	16.7(4)	0.84(0.35,2.00)	8.3(2)	1.69(0.43,6.74)

		Least severe		Intermediate	Most severe		Death	
	N	%(n)	RR(95%CI) *	%(n)	%(n)	RR(95%CI) *	%(n)	RR(95%CI) *
Wealth index								
1st qu. (richest)	102	36.3(37)	1.00	30.4(31)	23.5(24)	1.00	9.8(10)	1.00
2nd quarter	89	22.5(20)	0.57(0.37,0.85)	43.8(39)	24.7(22)	1.17 (0.74,1.86)	9.0(89)	1.09 (0.48,2.47)
3rd quarter	104	32.7(34)	0.80(0.59,1.08)	28.8(30)	31.7(33)	1.53 (1.03,2.27)	6.7(7)	0.82 (0.35,1.96)
4th qu. (poorest)	111	31.5(35)	0.83(0.62,1.11)	36.9(41)	20.7(23)	0.92 (0.58,1.47)	10.8(12)	1.15 (0.55,2.42)
Trend			0.96(0.86,1.08)			1.00 (0.88,1.14)		1.02 (0.8,1.29)
Tobacco								
Never smoker	241	26.1(63)	1.00	36.1(87)	27.8(67)	1.00	10.0(24)	1.00
Former smoker	48	27.1(13)	0.94(0.57,1.55)	29.2(14)	29.2(14)	0.98(0.58,1.65)	14.6(7)	1.65(0.70,3.93)
Current smoker	124	40.3(50)	0.98(0.69,1.37)	35.5(44)	18.5(23)	0.93(0.54,1.59)	5.6(7)	1.40(0.47,4.17)
Trend			0.99(0.83,1.17)			0.97(0.74,1.26)		1.22(0.72,2.08)
Alcohol consumed								
Not last year	258	24.0(62)	1.00	35.7(92)	29.1(75)	1.00	11.2(29)	1.00
Not last 30 days	46	30.4(14)	0.89(0.52,1.51)	50.0(23)	15.2(7)	0.60 (0.28,1.26)	4.4(2)	0.61 (0.14,2.73)
Not last 7 days	35	57.1(20)	1.48(0.95,2.29)	17.1(6)	14.3(5)	0.74 (0.33,1.65)	11.4(4)	2.05 (0.57,7.34)
In last 7 days	75	41.3(31)	1.06(0.7,1.63)	32.0(24)	22.7(17)	1.11 (0.67,1.85)	4.0(3)	0.73 (0.2,2.68)
Trend			1.11(0.98,1.26)			1.05 (0.87,1.27)		0.95 (0.64,1.43)
HBP (self-report)								
No	216	34.7(75)	1.00	32.9(71)	24.1(52)	1.00	8.3(18)	1.00
Yes	198	26.3(52)	0.99(0.74,1.32)	37.4(74)	26.3(52)	0.91(0.67,1.23)	10.1(20)	0.94(0.54,1.65)
Delayed admission								
No	305	30.2(92)	1.00	34.8(106)	25.9(79)	1.00	9.2(28)	1.00
Yes	109	32.1(35)	1.15(0.87,1.52)	35.8(39)	22.9(25)	0.82 (0.57,1.19)	9.2(10)	0.91(0.47,1.73)
High cholesterol								
No	122	32.0(39)	1.0	32.8(40)	23.8(29)	1.0	11.5(14)	1.0
Yes	291	30.2(88)	1.02(0.77, 1.34)	36.1(105)	25.8(75)	1.0 (0.72, 1.41)	7.9(23)	0.61(0.35, 1.08)

* RR(95%CI) = relative risk (95% confidence interval) adjusted for age and sex.

Table A4.3: Risk and relative risk of disability at three months following onset of first-ever stroke, and of death following first-ever stroke, in Ho Chi Minh City, Viet Nam, with conditioning on disability at baseline.

		Least severe (mRS=0/1)		Intermediate (mRS=2/3)	Most severe (mRS=4/5)		Death (mRS = 6)	
	N	%(n)	RR(95%CI) †	%(n)	%(n)	RR(95%CI) †	%(n)	RR(95%CI) †
Weight status								
Underweight	47	21.3(10)	1.00	31.9(15)	27.7(13)	1.00	19.1(9)	1.00
Normal	170	30.6(52)	1.09(0.68,1.75)	32.9(56)	26.5(45)	1.20(0.75,1.92)	10.0(17)	1.00(0.50,1.99)
Overweight	157	34.4(54)	1.13(0.71,1.82)	37.6(59)	21.7(34)	0.98(0.59,1.62)	6.4(10)	0.77(0.34,1.76)
Obese	39	25.6(10)	0.43(0.21,0.89)*	38.5(15)	30.8(12)	1.70(0.95,3.04)	5.1(2)	0.69(0.18,2.72)
Trend			0.90(0.77,1.04)			1.07(0.90,1.29)		0.87(0.64,1.19)
Education								
No schooling	134	17.9(24)	1.00	34.3(46)	30.6(41)	1.00	17.2(23)	1.00
Primary school	104	29.8(31)	1.00(0.62,1.62)	39.4(41)	24.0(25)	1.08(0.74,1.57)	6.7(7)	0.58(0.27,1.26)
Secondary school	79	39.2(31)	1.43(0.94,2.16)	32.9(26)	22.8(18)	1.33(0.83,2.16)	5.1(4)	0.45(0.12,1.63)
High school		39.7(25)	1.34(0.85, 2.10)	34.9(22)	20.6(13)	1.20(0.68, 2.14)	4.8(3)	0.54(0.14, 2.07)
College/ university		47.1(16)	2.20(1.35, 3.57)**	29.4(10)	20.6(7)	0.77(0.37, 1.57)	2.9(1)	0.28(0, 2.03)
Trend			1.19(1.07, 1.33)**			0.98(0.86, 1.12)		0.75(0.54, 1.04)
Working status ‡								
Manual work	70	47.1(33)	1.00	37.1(26)	12.9(9)	1.00	2.9(2)	1.00
Office work	74	47.3(35)	0.95(0.68,1.32)	35.1(26)	13.5(10)	1.15(0.53,2.50)	4.1(3)	1.60(0.28,9.13)
At home/retired	268	21.6(58)	0.77(0.53,1.11)	34.3(92)	31.7(85)	1.14(0.53,2.44)	12.3(33)	2.48(0.45,13.6)
Living with spouse								
Yes	240	36.7(88)	1.00	37.1(89)	21.3(51)	1.00	5.0(12)	1.00
No, with children	146	20.5(30)	1.13(0.79,1.62)	30.1(44)	33.6(49)	0.83(0.59,1.17)	15.8(23)	1.89(0.83,4.32)
No, with others	24	33.3(8)	1.06(0.64,1.74)	41.7(10)	16.7(4)	0.75(0.31,1.79)	8.3(2)	0.98(0.15,6.60)

	N	Least severe		Intermediate(		Most severe		Death	
		%(n)	RR(95%CI) †	%(n)		%(n)	RR(95%CI) †	%(n)	RR(95%CI) †
Wealth index									
1st qu. (richest)	102	36.3(37)	1.00	30.4%	(31)	23.5 (24)	1.00	9.8(10)	1.00
2nd quarter	89	22.5(20)	0.51(0.35,0.76)**	43.8%	(39)	24.7 (22)	1.14 (0.74,1.74)	9.0(89)	0.88 (0.40,1.96)
3rd quarter	104	32.7(34)	0.62(0.46,0.84)**	28.8%	(30)	31.7 (33)	1.83 (1.23,2.73)	6.7(7)	1.00 (0.42,2.37)
4th quarter	111	31.5(35)	0.72(0.54,0.95)*	36.9%	(41)	20.7 (23)	0.95 (0.61,1.48)	10.8(12)	1.16 (0.58,2.33)
Trend			0.94(0.84,1.06)				1.02 (0.90,1.15)		1.03 (0.82,1.30)
Tobacco									
Never smoker	241	26.1(63)	1.00	36.1(87)		27.8(67)	1.00	10.0(24)	1.00
Former smoker	48	27.1(13)	1.17(0.76,1.81)	29.2(14)		29.2(14)	0.86(0.49,1.51)	14.6(7)	2.22(0.66,7.49)
Current smoker	124	40.3(50)	1.00(0.73,1.36)	35.5(44)		18.5(23)	0.87(0.51,1.49)	5.6(7)	1.82(0.52,6.35)
Trend			0.99(0.86,1.15)				0.94(0.73,1.22)		1.24(0.72,2.14)
Alcohol consumed									
Not last year	258	24.0(62)	1.00	35.7(92)		29.1(75)	1.00	11.2(29)	1.00
Not last 30 days	46	30.4(14)	1.01(0.62,1.66)	50.0(23)		15.2(7)	0.62 (0.30,1.27)	4.4(2)	0.22 (0.04,1.06)
Not last 7 days	35	57.1(20)	1.56(1.00,2.40)*	17.1(6)		14.3(5)	0.93 (0.40,1.15)	11.4(4)	3.57 (0.73,18.09)
In last 7 days	75	41.3(31)	1.30(0.84,2.02)	32.0(24)		22.7(17)	0.96 (0.59,1.55)	4.0(3)	0.27 (0.07,1.07)
Trend			1.11(0.97,1.27)				0.99 (0.82,1.19)		0.79 (0.51,1.25)
HBP (self-report)									
No	216	34.7(75)	1.00	32.9(71)		24.1(52)	1.00	8.3(18)	1.00
Yes	198	26.3(52)	0.93(0.73,1.20)	37.4(74)		26.3(52)	1.00(0.75,1.34)	10.1(20)	1.08(0.63,1.83)
Delayed admission									
No	305	30.2(92)	1.00	34.8(106)		25.9(79)	1.00	9.2(28)	1.00
Yes	109	32.1(35)	1.10(0.85,1.42)	35.8(39)		22.9(25)	0.86 (0.60,1.23)	9.2(10)	1.08(0.56,2.07)
Hypercholesterol									
No	122	32.0(39)	1.0	32.8(40)		23.8(29)	1.0	11.5(14)	1.0
Yes	291	30.2(88)	0.93(0.73, 1.17)	36.1(105)		25.8(75)	1.11 (0.80, 1.55)	7.9(23)	0.73(0.41, 1.28)

* denotes p<0.05, ** denotes p<0.01, *** denotes p<0.001.

† RR(95%CI) = relative risk (95% confidence interval) adjusted for age, sex and modified Rankin Scale category at admission.

Table A4.4: Recovery of functional status over the three months of follow-up assessed in terms of change in functional status (mRS) scores.

Characteristic	N	Mean (SD)	Diff (95% CI)†
All patients	409	–0.50 (1.55)	
Age group			
< 45years	39	–1.41 (1.46)	ref
45–54years	95	–0.85 (1.43)	0.54 (0,1.08)*
55–64years	99	–0.84 (1.46)	0.55 (0,1.08)*
65–74years	80	–0.10 (1.46)	**1.27 (0.71,1.82)*** **
75+years	96	0.24 (1.47)	**1.51 (0.96,2.06)*** **
Trend			**0.37 (0.26,0.48)*** **
Sex			
Male	217	–0.78 (1.56)	ref
Female	192	–0.18 (1.48)	**0.37 (0.08,0.66)***
Education			
No schooling	133	–0.06 (1.56)	ref
Primary school	102	–0.57 (1.50)	–0.25 (–0.63,0.13)
Secondary school	78	–0.76 (1.57)	–0.18 (–0.62,0.25)
High school	96	–0.73 (1.51)	–0.10 (–0.57,0.38)
College/university			-0.39 (-0.97, 0.19)
Trend			–0.06 (–0.18,0.06)
Working status			
Manual work	70	–1.04 (1.47)	ref
Office work	73	–1.05 (1.46)	–0.12 (–0.60,0.36)
At home/retired	264	–0.19 (1.51)	0.10 (–0.35,0.56)
			P = 0.58‡
Living with spouse			
Yes	143	–0.79 (1.53)	ref
No, with children	22	0.01 (1.43)	0.17 (–0.20,0.54)
No, with others	4	–1.0 (1.41)	–0.31 (–0.94,0.32)
			P = 0.86‡
Wealth index			
1st qu. (richest)	104	–0.66 (1.44)	ref
2nd quarter	81	–0.27 (1.58)	0.38 (–0.04,0.80)
3rd quarter	104	–0.49 (1.63)	0.24 (–0.16,0.63)
4th quarter	109	–0.53 (1.58)	0.14 (–0.25,0.53)
Trend			0.03 (–0.09,0.16)
Tobacco smoking			
Never smoker	236	–0.34 (1.48)	ref
Former smoker	46	–0.39 (1.91)	0.14 (–0.40,0.68)
Current smoker	123	–0.87 (1.50)	0.07 (–0.36,0.51)
Trend			0.03 (–0.19,0.25)
Alcohol consumed			
Not last year	256	–0.25 (1.53)	ref
Not last 30 days	45	–0.76 (1.42)	–0.19 (–0.74,0.36)
Not last 7 days	34	–0.71 (1.62)	–0.07 (–0.54,0.67)
In last 7 days	75	–1.09 (1.50)	–0.35 (–0.84,0.13)
Trend			–0.10 (–0.26,0.06)

Characteristic	N	Mean (SD)	Diff (95% CI)[†]
HBP (self–report)			
No	215	–0.6 (1.55)	ref
Yes	194	–0.39 (1.55)	–0.06 (–0.34,0.23)
Comorbidity			
0	288	-0.66 (1.53)	ref
1	88	-0.15 (1.54)	0.34 (0, 0.68)
2+	33	-0.06 (1.54)	0.41 (-0.11, 0.93)
Trend			**0.25 (0.03, 0.47)[*]**
Pre-stroke disability			
No	379	–0.56 (1.54)	ref
Yes	30	0.33 (1.42)	0.54 (0, 1.08)[*]
Delayed admission			
No	301	–0.52 (1.59)	ref
Yes	108	–0.44 (1.45)	–0.11 (–0.43,0.21)
Type of stroke			
IS	312	–0.45 (1.56)	ref
ICH	97	–0.66 (1.50)	0.05 (–0.28,0.39)

[*] denotes p<0.05, [**] denotes p<0.01, [***] denotes p<0.001.

[†] Adjusted for age and sex but estimates for age adjusted for sex only and estimates for sex adjusted for age only.

[‡] Indicates p-value for differences

Chapter 5: Costs of first-ever stroke in Viet Nam

5.1. Preface

The previous chapters provided on the occurrence and clinical presentation of stroke and outcomes at three months after stroke onset in Viet Nam. Although early and three-month case-fatalities may be underestimated, the burden of stroke in Viet Nam seems to be substantial due to the severity of stroke at hospital admission and the severity of functional outcomes at three months. In this chapter, the burden of stroke is investigated in terms of its economic aspects. The data presented in this chapter were collected, during the period of hospitalisation of first-ever stroke patients in the cohort from electronic records of the hospital administration system and from patient interview. The text that follows in this Chapter and the Appendix 5 has been prepared for submission in consideration of publication in the Value in Health journal.

5.2. Introduction

Stroke was the second most common cause of death and the third most common cause of disability-adjusted life-years (DALYs) worldwide in 2010 [309]. The economic burden of stroke includes direct (medical and non-medical) and indirect (lost productivity or loss of income and caregiver burden) costs. These costs are specific to, and need to be estimated separately for, each country due to differences in hospital diagnostic procedures, treatment regimens and the costs assigned for resource use between countries [326,327].

The data describing the cost of stroke in low and middle income countries (LMICs) are limited [257]. In addition, most studies of the costs of stroke in LMICs have focused on direct costs without estimation of indirect costs. This is a major shortcoming for health system planning, because the burden of stroke has been estimated to be greater in LMICs than that in HICs due to higher incidence, prevalence, disability and case fatality in such countries [2]. Information on the cost of stroke is critical to assist policy makers in planning and prioritising the delivery of stroke care.

Viet Nam is a LMIC in south-east Asia that is undergoing epidemiological transition. Similar to other LMICs [27], stroke in Viet Nam occurs at younger ages [322] than in HICs. Currently, there are fewer than 10 stroke units in all of Viet Nam with a population of more than 80 million [293].. While we know that stroke severity is greater in Viet Nam than in other LMICs [12,28], there has been no study of the costs of stroke in Viet Nam.

The aims of this study were to estimate the societal costs of stroke, including direct medical costs of treatment and the associated direct non-medical and indirect costs incurred during hospitalisation in a stroke unit at a tertiary teaching hospital in Ho Chi Minh City.

5.3. Methods

Subjects

This cohort study was conducted in the stroke unit (Cerebrovascular Disease Department) of 115 People's Hospital, a major teaching hospital in Ho Chi Minh City, Viet Nam. Subject recruitment commenced on 1st June 2012 and continued until the targeted number of 10th September 2012. The study inclusion criteria were first-ever ischaemic or haemorrhagic stroke confirmed by a neurologist, age≥ 16 years, living in Ho Chi Minh City, occurrence within 7 days prior to admission, completion of acute stroke treatment in the stroke unit, and information available on direct medical costs of stroke treatment from hospital administration records.

Data collection

Clinical information was determined by a neurologist in the stroke unit on type of stroke, severity of impairment assessed on the National Institute Health Stroke Scale (NIHSS) [115] and severity of disability assessed on the modified Rankin Scale (mRS) [328]. Patients or their main caregivers were interviewed by research assistants to collect data on socio-demographic factors (marital status, education, occupation, working status), health insurance, economic status (household assets, monthly income per household, monthly expenditure per household), lifestyle risk factors (tobacco smoking, alcohol consumption) and health status before stroke (disability, co-morbidities including hypertension, diabetes, heart disease, chronic lung disease, chronic liver disease, chronic renal disease, cancer).

The bottom-up method [256] was used to estimate the costs of stroke. Medical cost data were extracted from electronic records of the hospital administration system. Data were classified into 9 categories (medication, laboratory tests, diagnostic imaging, consultant fees, bed-day fees, rehabilitation including physiotherapy and minor operations and procedures, medical consumables, special meals and feeding, other fees) for analysis. Direct non-medical costs included costs of in-hospital food for patients and caregivers, transportation costs from home to hospital and return for caregivers, and other sundry expenses. These costs were collected by daily interviews of patients or their caregivers. The indirect costs included loss of income of patients and caregivers during the period of treatment in the hospital. It was estimated as the product of income foregone per day by patients and caregivers, and the length of stay in the hospital. This cost was zero for patients and caregivers who were retired, in unpaid work or unemployed. The total costs of stroke treatment in a stroke unit in this study were the sum of direct medical cost, direct non-medical cost and indirect cost. The source of money used in payment of costs was determined by interviewing the patients or caregivers.

Data analysis

Severity of stroke assessed on the NIHSS with 42 as maximum was categorized into two groups as severe stroke (NIHSS > 7) and non-severe stroke (NIHSS ≤ 7) [329]. Disability assessed on the mRS with 5 as maximum for survivors was grouped into 3 categories of least severe (mRS=0/1), intermediate (mRS=2/3) and more severe (mRS=4/5). Socio-economic status was assessed from the holdings in the household of each patient of assets included in

the list of 2010 for Ho Chi Minh City published by the General Statistics Office of Viet Nam. A weighted sum of the assets held was calculated, with weights derived from the regression coefficient for each asset from the linear regression of household expenditure on binary (0=asset not held / 1=asset held) predictors for each asset in the list. Unit costs were converted from Vietnamese currency (Viet Nam Dong, VND) to US dollars using the general purchasing power parities (PPPs) index. This index measures the purchasing power of different national currencies, and is recommended for comparing costs across countries [326,330].

Summary values of continuous data are presented as median and interquartile range (IQR) and/or as mean and standard deviation (SD). Linear regression methods were used to compare means after transformation (e.g. by taking logarithms) of the right-skewed cost data. Summary values of categorical data are presented as percentages. Poisson regression with robust standard errors [331] and log multinomial regression [312] were used to estimate relative risk for binary and multinomial outcome data respectively. Confounding was assessed by the 10% change-in-parameter-estimate method [332]. Statistical interaction was assessed from the coefficient and standard error of the covariate formed as the product of the covariates for the study factor and the potential mediator, or by multivariate tests of multiple product terms. The fit of each final model was carefully assessed, and covariates were rescaled where necessary to improve fit. All statistical tests were two-sided with a 5% allowance for type I error.

5.4. Results

Characteristics of patients

Four hundred and fifty patients were ascertained from records of 960 admissions to the stroke unit from 1 June 2012 until 10 September 2012. We excluded 322 recurrent cases of stroke, and 58 persons with severe conditions who were discharged to home at the request of the family (probable deaths). Clinical records were unavailable for these severely-affected patients. After 9 deaths prior to enrolment, and exclusion of 4 cases without comprehensive information on direct medical costs, 437 patients provided data on hospital treatment costs.

Characteristics of the 437 patient participants in this cohort study are summarised in **Table 5.1**. They comprised 52.4% (229/437) males. The mean age was 62.4 years (IQR 52-74 years) for all patients. Around three times as many male patients as female patients had proceeded beyond primary school. Three quarters of the women were involved in home duties or had retired. Greater proportions of female patients than of male patients were widowed and living with children (**Table A5.1** in Appendix 5). The most common age groups were 45-64 years for men, and at 55-64 years for females.

Ischaemic stroke accounted for 76.0% (332/437) of the cases and was slightly more common among females than among males. Severity of impairment at admission assessed by mean NIHSS score was 8.2 (SD 5.8). The median NIHSS score was 6.0 (IQR 4-12). Female patients had greater severity of impairment at admission than male patients.

Regarding functional status at admission, the mean mRS score was 3.2 (SD 1.1; median 3.0, IQR 3-4). There were only minor differences by sex in these clinical characteristics (**Table 5.1**). Overall, 53.8% of patients (54.6% for male patients and 52.9% for female patients) had health insurance that provided co-payment for hospital costs, and 21.7% of patients had at least one comorbidity (**Table 5.1**).

Table 5.1: Characteristics of participants in the follow-up study of stroke patients admitted to 115 Hospital in Ho Chi Minh City, Viet Nam.

	Men (N=229)	Women (N=208)
Age		
Mean (SD*)	59.5 (12.8)	65.8 (14.5)
Median (IQR†)	58 (50–69)	68 (55–77)
< 45 years	11.8% (27/229)	7.2% (15/208)
45–54 years	26.6% (61/229)	17.3% (36/208)
55–64 years	26.6% (61/229)	21.6% (45/208)
65–74 years	21.8% (50/229)	18.8% (39/208)
75+ years	13.1% (30/229)	35.1% (73/208)
Highest education level‡		
< Primary	11.3% (24/213)	43.1% (81/188)
Primary school	24.4% (52/213)	31.9% 60/188)
Secondary school	25.4% (54/213)	16.0% (30/188)
Higher secondary	24.4% (53/213)	6.9% (13/188)
College/university	14.5% (31/213)	2.1% (4/188)
Working status‡		
Manual work	26.0% (59/227)	5.3% (11/208)
Office work	19.8% (45/227)	16.8% (35/208)
Home duties/retired	54.2% (123/227)	77.9% (162/208)
Living with spouse‡		
Yes	76.7% (173/227)	36.6% (75/205)
No – living with children	17.6% (40/227)	56.1% (115/205)
No – living with others	5.7% (13/227)	7.3% (15/205)
Type of stroke		
Ischaemic stroke (IS)	72.9% (167/229)	79.3% (165/208)
Intra-cerebral haemorrhage (ICH)	27.1% (62/229)	20.6% (43/208)
Impairment at admission (NIHSS§)		
Mean (SD*)	7.6 (5.4)	8.8 (6.1)
Not severe (NIHSS≤7)	58.6% (130/222)	51.8% (102/197)
Severe (NIHSS>7)	41.4% (92/222)	48.2% (95/197)
Functional status at admission (mRS)		
Mean (SD*)	3.1 (1.1)	3.2 (1.1)
Least severe (mRS=0/1)	11.0% (25/227)	10.8% (22/204)
Intermediate (mRS=2/3)	41.9% (95/227)	36.8% (75/204)
More severe (mRS=4/5)	47.1% (107/227)	52.5% (107-204)
Length of stay (days)		
Mean (SD*)	6.7 (4.4)	6.4 (4.1)
0–4 days	34.1% (74/229)	35.1% (73/208)
5–7 days	38.0% (87/229)	36.1% (75/208)
8+ days	28.0% (64/229)	28.9% (60/208)

* SD = standard deviation, † IQR = interquartile range, ‡ Patient self-report
§ NIHSS= National Institutes of Health Stroke Scale.

When household assets were considered, relatively more participants lived in households holding each category of household asset in the list of 2010 for Ho Chi Minh City published by the General Statistics Office of Viet Nam (**Table A5.2** in Appendix 5) compared with the general population of Ho Chi Minh City, suggesting that participants were drawn from a relatively affluent sub-population. In addition, the median per adult household income of 25–64 year old participants was nearly 50% greater than that of 25-64 year olds in the general population of Ho Chi Minh City (**Table A5.2** in Appendix 5). Conversely, patients with stroke aged 25–64 years had lower levels of educational attainment than their counterparts in the general population.

Direct medical costs

Table 5.2 shows that the mean direct medical costs per stroke patient were USD 560 [SD 562; median 385, IQR (285, 565)]. The mean hospital costs per day for each patient were USD 93.1 [SD 81.6; median 72.0, (IQR 56.1, 97.9)]. Other than for the very youngest patients, mean costs increased with age and, adjusted for age and sex, with the number of co-morbidities, severity of impairment, severity of disability and LOS.

The associations were reduced by adjusting, where relevant, for severity of impairment and LOS. Adjusted for age and sex, costs were higher on average for patients with ICH but this was reversed after adjustment for severity of impairment and LOS. The direct medical costs incurred were progressively lower for patients with lesser wealth irrespective of age and sex, and this association was attenuated but not removed by adjustment for severity of impairment and LOS.

Distribution of total costs and out-of-pocket costs of patients

The greatest contributors to direct medical costs were diagnostic imaging (approximately 32% of average costs and 36% of median costs) and bed-day fees (23%) (**Table 5.3**). After insurance co-payments were taken into account, these items remained the greatest contributors to median out-of-pocket costs with bed-day fees contributing relatively more of the total because insurance co-payments provided comparatively little reimbursement. Insurance provided assistance with four lower-cost items – medical consumables, medications, lab tests and rehabilitation – and with costs of diagnostic imaging, but made no or almost no contribution to the costs of the other items. The mean total out-of-pocket costs per patients were USD 380 (SD 389; median 275, IQR 155, 449) USD. The mean out-of-pocket costs per day were USD 64.0 (SD 62.8; median 50.2, IQR 29.2, 74.2).

The trend for less wealthy patients to incur lower direct medical costs (**Table 5.2**) was replicated for most of the categories in **Table 5.3** and, after adjustment for age and sex, was statistically significant for diagnostic imaging (p=0.014). The main exception to this was consultant fees that were higher on average for patients in lower wealth categories (trend p=0.016). Regarding the out-of-pocket component, less wealthy patients incurred lower bed-day fees (trend p=0.05) partly explained by their generally less severe condition (trend p=0.153 adjusted additionally for severity of impairment), but higher consultant fees (p=0.005) and higher costs of lab testing (p=0.023).

Table 5.2: Direct medical costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with putative explanatory factors.

	LOS (days)	Mean costs (USD) and ratios of means			
	Mean(SD)	Median (IQR)	Mean (SD)	Ratio (95% CI)*	Ratio (95% CI)†
All patients	6.6(4.2)	385 (282,565)	560 (562)		
Sex					
Male	6.7(4.4)	391 (271, 557)	565 (576)	1.00	1.00
Female	6.4(4.0)	384 (287, 568)	554 (548)	0.97 (0.87, 1.08)	0.97 (0.88, 1.06)
Age group					
<45 years	7.2(4.6)	438 (302, 537)	580 (582)	1.00	1.00
45-54 years	6.1(4.2)	356 (269, 479)	467 (376)	0.85 (0.68, 1.02)	0.95 (0.79, 1.11)
55-64 years	5.9(3.6)	358 (258, 506)	476 (393)	0.82 (0.66, 0.98)	0.94 (0.78, 1.09)
65-74 years	6.5(3.6)	379 (286, 545)	557 (561)	0.93 (0.74, 1.12)	1.00 (0.83, 1.17)
75+ years	7.4(5.1)	464 (296, 876)	728 (780)	1.11 (0.88, 1.34)	1.09 (0.91, 1.28)
Trend				**P = 0.01**	P = 0.09
Wealth index					
4th quarter (richest)	6.9(4.8)	470 (287,780)	679 (662)	1.00	1.00
3rd quarter	6.5(3.9)	374 (286, 544)	528 (433)	0.88 (0.75, 1.02)	0.95 (0.83, 1.07)
2nd quarter	6.5(4.1)	376 (271, 541)	546 (575)	**0.85 (0.71, 0.97)**	**0.87 (0.76, 0.97)**
1st quarter (poorest)	6.3(4.0)	368 (274, 483)	499 (546)	**0.82 (0.70, 0.94)**	**0.88 (0.77, 0.98)**
Trend				**P = 0.04**	**P = 0.01**
Health insurance					
No	6.3(3.8)	384 (286, 534)	533 (441)	1.00	1.00
Yes	6.7(4.6)	385 (272, 578)	583 (649)	0.96 (0.85, 1.06)	0.93 (0.84, 1.00)
Comorbidity					
No comorbidity	6.4(4.2)	357 (273, 522)	513 (475)	1.00	1.00
1 comorbidity	6.1(2.9)	446 (294, 621)	573 (508)	**1.14 (0.99, 1.29)**	1.12 (1.00, 1.24)
2-6 comorbidities	8.5(6.2)	428 (323, 1040)	934 (1058)	**1.35 (1.06, 1.63)**	1.17 (0.97, 1.36)
Trend				**P = 0.03**	**P = 0.02**

	LOS (days)	Mean costs (USD) and ratios of means			
	Mean(SD)	Median (IQR)	Mean (SD)	Ratio (95% CI)[*]	Ratio (95% CI)†
Type of stroke					
Intracerebral haemorrhage	8.7(5.9)	433 (302, 605)	637 (691)	1.00	1.00
IS[‡]	5.9(3.3)	366 (276, 542)	535 (514)	**0.88 (0.77, 0.99)**	**1.17 (1.04, 1.30)**
IS[§]	5.8(3.3)	346 (274, 506)	458 (369)	**0.83 (0.73, 0.93)**	1.09 (0.98, 1.20)
Severity of impairment [¶]					
Not severe (NIHSS ≤ 7)	5.5(3.4)	308 (263, 452)	390 (256)	1.00	1.00
Severe (NIHSS > 7)	7.9(4.8)	506 (346, 941)	786 (754)	**1.54 (1.38, 1.71)**	**1.33 (1.20, 1.45)**
Severity of disability[#]					
Least severe (mRS 0/1)	5.1(3.0)	300 (251, 429)	373 (205)	1.00	1.00
Intermediate (mRS 2/3)	5.6(3.5)	309 (273, 456)	424 (363)	1.04 (0.88, 1.20)	0.96 (0.82, 1.10)
Most severe (mRS 4/5)	7.7(4.7)	479 (316, 876)	713 (698)	**1.45 (1.22, 1.68)**	1.03 (0.85, 1.20)
Trend				**P < 0.01**	P = 0.53
Length of stay					
0-4 days	NA	269 (243, 391)	362 (378)	1.00	1.00
5-7 days		568 (403, 905)	807 (715)	**2.00 (1.78, 2.21)**	**1.76 (1.57, 1.95)**
8+ days		344 (293, 502)	478 (377)	**1.31 (1.18, 1.44)**	**1.29 (1.16, 1.43)**
Trend				**P < 0.01**	**P < 0.01**

[*] Ratio of means (95% confidence interval) adjusted for age and sex.
† Ratio of means (95% confidence interval) adjusted for age, sex, severity of impairment.
‡ Including including cost of thrombolitic treatment.
§ Excluding cost of thrombolitic treatment.
¶ Severity of impairment assesed on the National Institutes of Health Stroke Scale (NIHSS) scale..
# Severity of disability assessed on the modified Rankin Scale (mRS).

Table 5.3: Distribution of direct medical costs.

Item	Total cost				Patient out-of-pocket cost			Out-of-pocket as % of total cost
	n	mean (SD)	%	median (IQR)	n	median (IQR)	%	
Consultant fees	430	1.4 (1.1)	0.2	1.5 (0.3, 1.5)	417	1.5 (0, 1.5)	0.5	100.0
Bed-day fees	437	127.2 (117.3)	22.7	93.2 (62.1, 139.8)	436	88.2 (62.1, 139.8)	32.0	94.6
Lab tests	437	58.0 (28.4)	10.4	51.5 (44.8, 59.3)	422	33.5 (10.0, 50.3)	12.2	65.0
Diagnostic imaging	436	178.8 (99.8)	31.9	138.6 (117.5, 228.2)	429	98.2 31.4, 148.6)	35.6	70.9
Rehabilitation*	174	54.5 (221.8)	9.7	12.4 (6.3, 27.9)	169	8.1 (2.7, 15.5)	2.9	65.3
Medications	436	147.5 (351.3)	26.3	26.5 (14.5, 68.1)	419	14.0 (4.1, 33.5)	5.1	52.8
Medical consumables	314	11.3 (16.7)	2.0	6.5 (1.8, 13.9)	306	2.5 (0.8, 9.3)	0.9	38.5
Meals and feeding†	15	35.4 (23.4)	6.3	26.4 (22.2, 49.7)	15	26.4 (22.2, 49.7)	9.6	100.0
Other	437	15.3 (10.9)	2.7	11.7 (8.5, 18.7)	437	11.7 (8.5, 18.7)	4.2	100.0
Total	437	560.2 (562.8)	100.0	385.6 (282.7, 566.1)	437	275.6 (155.7, 449.6)	100.0	49.2

* includes physiotherapy and costs of minor surgical procedure
†included special diet and feeding

Table 5.4: Distribution of out-of-pocket expenditure on direct medical costs.

	Uninsured patient			Insured patient			Ratio of means
	n	mean (SD)	median (IQR)	n	mean (SD)	median (IQR)	Ratio (95% CI)
Consultant fees	198	2.01 (1.2)	1.5 (1.5, 2.0)	219	0.7 (1.0)	0.06 (0.06, 1.5)	**0.19 0.14, 0.23)**
Bed-day fees	202	126.9 (115.8)	93.2 (62.1, 139.8)	234	122.3 (115.7)	87.3 (58.8, 133.2)	0.94 (0.82, 1.05)
Lab tests	202	54.5 (19.8)	50.3 (44.6, 56.7)	220	12.4 (12.5)	10.0 (7.8, 11.4)	**0.19 (0.17, 0.21)**
Diagnostic imaging	202	187.4 (105.1)	148.6 (126.9, 247.0)	227	53.8 (54.2)	41.6 (22.2, 62.1)	**0.23 0.20, 0.27)**
Rehabilitation*	77	22.9 (39.3)	10.9 (6.6, 20.7)	92	51.6 (279.1)	3.6 (2.0, 11.4)	0.90 (0.43, 1.37)
Medications	202	127.4 (286.5)	24.2 (14.8, 62.4)	217	24.7 (63.2)	4.8 (2.2, 11.4)	**0.16 (0.11, 0.20)**
Medical consumables	161	9.2 (10.6)	5.5 (1.4, 13.3)	145	5.2 (12.7)	1.2 (0.4, 3.6)	**0.30 (0.20, 0.41)**
Meals and feeding†	6	52.8 (27.1)	51.0 (27.4, 74.5)	9	23.8 (11.1)	23.3 (16.0, 25.8)	**0.47 (0.20, 0.74)**
Other	202	14.9 (9.5)	11.4 (8.5, 18.1)	235	15.7 (12.1)	11.9 (8.5, 19.3)	1.00 (0.90, 1.11)
Total	202	533.7 (441.9)	384.7 (286.6, 534.3)	235	249.6 (277.5)	167.5 (118.4, 277.3)	0.40 (0.36, 0.44)

* Includes physiotherapy and costs of minor surgical procedure

† Includes special diet and feeding

Health insurance

Insured patients were generally older ($p<0.001$), had greater wealth ($p=0.008$) and larger numbers of comorbidities ($p=0.002$) (**Table 5.4**). Their severity of impairment was 0.86 points greater ($p=0.13$) on the NIHSS scale, and their LOS was longer ($p=0.30$) by 0.42 days, but these differences did not reach statistical significance. The direct medical cost of insured patients was 9.8% (95% CI 1.7%, 17.9%) lower than that of non-insured patients after adjustment for age, sex, wealth, comorbidity, severity of impairment (NIHSS) and LOS. Significantly lower costs were incurred by insured patients for diagnostic imaging ($p=0.008$) and bed-day fees ($p=0.02$). Out-of-pocket costs were greater on average for patients without health insurance (USD 533 (SD 441) than for patients with health insurance (USD 249 (SD 277), $p<0.01$. Out-of-pocket expenditure was 71.3% of total direct treatment costs for all stroke patients, and 43.4% of total direct treatment costs for insured patients. Only for bed-day fees, rehabilitation and other costs did health insurance not result in a statistically significant reduction in total direct treatment costs that had to be met out-of-pocket.

Direct non-medical costs

The majority of patients (98.2%) incurred some direct non-medical costs (**Table 5.5**). The characteristics of patients (n=429) who incurred these costs were not distinguishable from those of patients (n=8) who did not. The mean costs incurred were USD 171 (SD 486; median 105, IQR 67, 169). The direct medical costs incurred were greater for patients with ICH (but not after adjustment for severity of impairment and LOS), for those with more severe impairment, for those with more severe disability (but not after adjustment for severity of impairment and LOS), and for those whose LOS exceeded 4 days.

Indirect costs

Patients who incurred indirect costs tended to be younger and have lesser comorbidity than patients who did not incur these costs (**Table 5.6**). The average costs incurred were USD 240 (SD 392; median 124, IQR 53, 2498). Indirect medical costs were greater on for younger patients, those who were wealthier, those with ICH, those with more severe impairment, those with greater disability (but not after adjustment for severity of impairment and LOS), and those whose LOS exceeded 4 days.

Total costs

Mean total costs were USD 963 (SD 968; median 684, IQR 467, 1047) (**Table 5.7**). Non-medical costs, including direct non-medical cost and indirect cost, contributed 33.6% of total cost for all stroke patients. The total costs were greater for patients who were wealthier, those with comorbidity and those with ICH (but not in either case after adjustment for severity of impairment and LOS), those with more severe impairment, those with greater disability (but not after adjustment for severity of impairment and LOS), and those whose LOS exceeded 4 days. Results are shown for the wealth index, but total costs were also positively associated with average monthly income of household ($p=0.01$) and with their average monthly expenditure ($p<0.001$).Information collected on the sources of money used in payment of costs indicated that 51.5% (225/434) of patients used family savings, 72.5% (317/434) used money provided by relatives, 8.5% (37/434) borrowed money from other sources, and 0.9% (4/434) sold family assets to pay the hospital fee.

Table 5.5: Direct non-medical costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with putative explanatory factors.

	Patients who incurred cost		Cost incurred			
				Mean cost and ratio of means		
	% (n/N)	RR (95% CI) *	Median (IQR)	Mean (SD)	Ratio (95% CI)†	Ratio (95% CI)‡
All patient			105 (67, 169)	171 (486)		
Sex						
Male	97.4%(223/229)	1.00	104 (63, 156)	179 (633)	1.00	1.00
Female	99.0%(206/208)	1.02(0.99, 1.04)	106 (69, 171)	162 (241)	1.08 (0.90, 1.25)	1.04 (0.89, 1.20)
Age group						
< 45 years	100.0%(42/42)	1.00	98 (63, 173)	147 (161)	1.00	1.00
45-54 years	100.0%(97/97)		93 (67, 150)	223 (949)	0.98 (0.68, 1.28)	1.12 (0.80, 1.43)
55-64 years	96.2%(102/106)		96 (61, 146)	124 (105)	0.85 (0.59, 1.11)	1.04 (0.75, 1.33)
65-74 years	96.6%(86/89)	0.98(0.94, 1.02)	118 (71, 193)	172 (179)	1.12 (0.77, 1.47)	1.20 (0.86, 1.55)
75+ years	99.0%(102/103)	1.01(0.98, 1.03)	115 (74, 201)	179 (301)	1.12 (0.77, 1.46)	1.08 (0.78, 1.39)
Trend		P = 0.19			P = 0.17	P = 0.58
Wealth index						
4th quarter (richest)	97.2% (104/107)	1.00	114 (65, 200)	153 (127)	1.00	1.00
3rd quarter	97.8% (90/92)	1.00 (0.96, 1.05)	106 (68, 207)	268 (991)	1.07 (0.81, 1.32)	1.11 (0.87, 1.35)
2nd quarter	98.2% (110/112)	1.01 (0.97, 1.05)	106 (68, 170)	170 (298)	0.98 (0.75, 1.21)	1.01 (0.81, 1.22)
1st quarter (poorest)	99.2% (117/118)	1.02 (0.98, 1.06)	100 (63, 145)	114 (88)	0.82 (0.64, 1.01)	0.88 (0.70, 1.06)
Trend		P = 0.28			P = 0.06	P= 0.13
Health insurance						
No	99.0% (200/202)	1.00	99 (66, 154)	184 (668)	1.00	1.00
Yes	97.5% (229/235)	0.98 (0.96, 1.00)	109 (68, 172)	160 (229)	1.03 (0.86, 1.20)	1.01 (0.86, 1.16)

	Patients who incurred cost		Cost incurred			
				Mean cost and ratio of means		
	% (n/N)	RR (95% CI) *	Median (IQR)	Mean (SD)	Ratio (95% CI)†	Ratio (95% CI)‡
Comorbidity						
No comorbidity	98.7% (306/310)	1.00	104 (66, 163)	181 (569)	1.00	1.00
1 comorbidity	97.8% (89/91)	0.99 (0.96, 1.02)	95 (63, 159)	133 (138)	0.89 (0.71, 1.07)	0.89 (0.72, 1.05)
2-6 comorbidities	94.4% (34/36)	0.96 (0.88, 1.04)	172 (106, 259)	184 (110)	1.39 (0.97, 1.82)	1.20 (0.87, 1.54)
Trend		P = 0.24			P = 0.31	P = 0.74
Type of stroke						
IS	98.8% (328/332)	1.00	97 (62, 153)	127 (112)	1.0	1.00
ICH	96.2% (101/105)	0.97 (0.94, 1.01)	138 (87, 255)	314 (971)	**1.71 (1.39, 2.03)**	1.23 (1.0, 1.47)
Severity of impairment¶						
Not severe (NIHSS ≤ 7)	98.7% (229/232)	1.00	91 (62, 129)	149 (621)	1.0	1.00
Severe (NIHSS > 7)	97.9% (183/187)	0.99 (0.97, 1.02)	137 (77, 231)	192 (254)	**1.55 (1.30, 1.80)**	**1.29 (1.09, 1.50)**
Severity of disability#						
Least severe (mRS 0/1)	100.0% (47/47)		87 (63, 104)	82 (42)	1.00	1.00
Intermediate (mRS 2/3)	98.8% (168/170)	1.00	95 (62, 148)	175 (724)	**1.36 (1.00, 1.72)**	1.22 (0.92, 1.53)
Most severe (mRS 4/5)	97.2% (208/214)	0.98 (0.96, 1.00)	124 (77, 217)	188 (250)	**1.86 (1.40, 2.34)**	1.21 (0.87, 1.55)
Trend		P = 0.07			**P < 0.001**	**P = 0.32**
Length of stay						
0-4 days	98.0% (148/151)	1.00	77 (49, 108)	89 (80)	1.00	1.00
5-7 days	98.2% (159/162)	1.00 (0.97, 1.03)	156 (92, 292)	281 (779)	**2.29 (1.89, 2.69)**	**1.94 (1.58, 2.29)**
8+ days	98.4% (122/124)	1.00 (0.97, 1.04)	108 (74, 153)	127 (90)	**1.48 (1.21, 1.76)**	**1.40 (1.14, 1.65)**
Trend		P = 0.82			**P < 0.001**	**P = 0.001**

* Relative risk (95% confidence interval) ; † Ratio of means (95%CI) adjusted for age, sex.

‡ Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.

¶ Severity of impairment assessed on the National Institutes of Health Stroke Scale (NIHSS); # Severity of disability assessed on the modified Rankin Scale (mRS).

Table 5.6: Indirect costs (USD) of stroke patients (loss of income of patients and their caregivers) at 115 People's Hospital, Ho Chi Minh City, and associations with putative explanatory factors.

	Patients who incurred cost		Cost incurred			
				Mean costs and ratio of means		
	% (n/N)	RR (95% CI) *	Median (IQR)	Mean (SD)	Ratio (95% CI)†	Ratio (95% CI)‡
All patient			124(53, 2498)	240(392)		
Sex						
Male	70.3%(161/229)	1.00	124(6, 259)	265(456)	1.00	1.00
Female	72.6%(151/208)	1.03(0.92, 1.16)	114(49, 249)	214(309)	0.98(0.71, 1.25)	0.86(0.63, 1.09)
Age group						
<45 years	92.9%(39/42)	1.00	145(78, 259)	261(374)	1.00	1.00
45-54 years	82.5%(80/97)	0.89(0.78, 1.00)	132(78, 236)	247(445)	1.00(0.54, 1.46)	1.10(0.61, 1.60)
55-64 years	73.6%(78/106)	0.79(0.69, 0.91)	91(41, 259)	256(453)	0.81(0.43, 1.19)	0.97(0.53, 1.41)
65-74 years	55.1%(49/89)	0.59(0.48, 0.73)	134(50, 326)	213(227)	0.86(0.42, 1.29)	0.84(0.43, 1.24)
75+ years	64.1%(66/103)	0.69(0.58, 0.82)	93(31, 223)	220(361)	0.69(0.35, 1.02)	0.70(0.37, 1.02)
Trend		**P < 0.001**			P = 0.05	**P = 0.02**
Wealth index						
4th quarter (richest)	66.4% (71/107)	1.00	165(62, 528)	378(544)	1.00	1.00
3rd quarter	77.2% (71/92)	1.16 (0.98, 1.39)	145(52, 316)	283(431)	0.85(0.52, 1.19)	0.88(0.55, 1.21)
2nd quarter	75.9% (85/112)	1.14 (0.96, 1.36)	108(52, 221)	166(170)	**0.61(0.39, 0.85)**	**0.62(0.40, 0.85)**
1st quarter (poorest)	67.8% (80/118)	1.02 (0.85, 1.23)	99(41, 176)	166(341)	**0.55(0.34, 0.76)**	**0.62(0.39, 0.85)**
Trend		P = 0.89			**P < 0.001**	**P = 0.001**
Health insurance						
No	72.8% (147/202)	1.00	102(50, 225)	228(423)	1.00	1.00
Yes	70.2% (165/235)	0.96 (0.86, 1.09)	138(62, 259)	251(363)	1.22(0.89, 1.56)	1.17(0.82, 1.41)

	Patients who incurred cost		Cost incurred			
				Mean costs and ratio of means		
	% (n/N)	RR (95% CI) *	Median (IQR)	Mean (SD)	Ratio (95% CI)†	Ratio (95% CI)‡
Comorbidity						
No comorbidity	74.8% (232/310)	1.00	124(52, 242)	257(436)	1.00	1.00
1 comorbidity	63.7% (58/91)	0.85 (0.72, 1.00)	99(51, 249)	178(179)	0.95(0.62, 1.28)	0.97(0.64, 1.30)
2-6 comorbidities	61.1% (22/36)	0.82 (0.62, 1.07)	121(71, 259)	230(285)	1.18(0.55, 1.79)	1.11(0.55, 1.68)
Trend		**P = 0.03**			P = 0.77	P = 0.83
Type of stroke						
IS	70.2% (233/332)	1.00	103(50, 228)	220(365)	1.00	1.00
ICH	75.2% (79/105)	1.07 (0.94, 1.22)	155(83, 373)	301(460)	1.34(0.92, 1.76)	0.97(0.65, 1.30)
Severity of impairment¶						
Not severe (NIHSS ≤ 7)	72.0% (167/232)	1.00	93(38, 207)	182(324)	ref	1.00
Severe (NIHSS > 7)	71.1% (133/187)	0.99 (0.87, 1.12)	158(73, 378)	315(463)	**1.85(1.35, 2.35)**	**1.60(1.17, 2.03)**
Severity of disability#						
Least severe (mRS 0/1)	59.6% (28/47)	1.00	98(46, 219)	162(171)	ref	1.00
Intermediate (mRS 2/3)	75.3% (128/170)	1.26 (0.98, 1.62)	90(41, 197)	209(409)	0.96(0.50, 1.42)	0.80(0.42, 1.17)
Most severe (mRS 4/5)	71.0% (152/214)	1.19 (0.93, 1.53)	150(69, 357)	284(407)	1.52(0.79, 2.26)	0.92(0.44, 1.40)
Trend		P= 0.49			**P = 0.02**	P = 0.93
Length of stay						
0-4 days	68.9% (104/151)	1.00	80(31, 145)	150(270)	ref	1.00
5-7 days	68.5% (111/162)	1.00 (0.86, 1.16)	186(73, 466)	358(538)	**2.26(1.56, 2.96)**	**1.74(1.17, 2.32)**
8+ days	78.2% (97/124)	1.14 (0.99, 1.31)	124(57, 223)	202(249)	**1.49(1.02, 1.96)**	1.39(0.94, 1.83)
Trend		P= 0.09			**P = 0.03**	P = 0.07

* Relative risk (95% confidence interval); † Ratio of means (95%CI) adjusted for age, sex.
‡ Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS; ¶ Severity of impairment assessed on the National Institutes of Health Stroke Scale (NIHSS);
# Severity of disability assessed on the modified Rankin Scale (mRS).

Table 5.7: Total costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with putative explanatory factors.

		Mean costs and ratios of means		
	Median (IQR)	Mean (SD)	Ratio (95% CI)*	Ratio (95% CI)†
All patient	619 (424, 1012)	901 (903)		
Sex				
Male	634 (432, 1025)	928 (978)	1.00	1.00
Female	616 (417, 1002)	871 (814)	0.99 (0.87, 1.10)	0.96 (0.87, 1.04)
Age group				
< 45 years	677 (439, 1248)	971 (812)	1.00	1.00
45-54 years	617 (450, 892)	895 (1122)	0.90 (0.70, 1.10)	1.00 (0.82, 1.18)
55-64 years	574 (374, 912)	785 (671)	0.80 (0.62, 0.97)	0.93 (0.76, 1.09)
65-74 years	617 (417, 974)	842 (681)	0.89 (0.69, 1.09)	0.94 (0.77, 1.11)
75+ years	723 (471, 1141)	1047 (1063)	1.05 (0.81, 1.29)	1.00 (0.82, 1.18)
Trend			P = 0.29	P = 0.85
Wealth index				
4th quarter (richest)	758 (471, 1284)	1079 (872)	1.00	1.00
3rd quarter	667 (430, 997)	1011 (1200)	0.89 (0.74, 1.04)	0.97 (0.84, 1.11)
2nd quarter	606 (413, 907)	840 (873)	**0.81 (0.68, 0.94)**	**0.83 (0.73, 0.94)**
1st quarter (poorest)	539 (411, 771)	727 (650)	**0.74 (0.62, 0.85)**	**0.80 (0.70, 0.90)**
Trend			**P < 0.001**	**P < 0.001**
Health insurance				
No	604 (417, 953)	883 (933)	1.00	1.00
Yes	665 (439, 1047)	916 (878)	1.03 (0.91, 1.15)	0.99 (0.90, 1.09)

	Median (IQR)	Mean costs and ratios of means		
		Mean (SD)	Ratio (95% CI)*	Ratio (95% CI)†
Comorbidity				
No comorbidity	601 (417, 953)	884 (940)	1.00	1.00
1 comorbidity	649 (413, 983)	818 (609)	1.02 (0.87, 1.16)	1.00 (0.88, 1.11)
2-6 comorbidities	878 (565, 1407)	1250 (1118)	1.35 (1.04, 1.66)	1.13 (0.93, 1.33)
Trend			**P = 0.04**	P = 0.32
Type of stroke				
IS	599 (411, 932)	817 (680)	1.00	1.00
ICH	722 (500, 1254)	1166 (1361)	**1.27 (1.09, 1.45)**	0.92 (0.81, 1.03)
Severity of impairment¶				
Not severe (NIHSS≤ 7)	502 (386, 738)	670 (755)	1.00	1.00
Severe (NIHSS> 7)	847 (593, 1522)	1199 (1012)	**1.63 (1.45, 1.82)**	**1.38 (1.24, 1.52)**
Severity of disability#				
Least severe (mRS 0/1)	421 (386, 680)	552 (275)	1.00	1.00
Intermediate (mRS 2/3)	542 (385, 744)	756 (914)	1.14 (0.95, 1.33)	1.03 (0.87, 1.19)
Most severe (mRS 4/5)	768 (545, 1324)	1099 (950)	**1.61 (1.34, 1.89)**	1.08 (0.89, 1.27)
Trend			**P < 0.001**	P = 0.38
Length of stay				
0-4 days	424 (343, 592)	554 (487)	1.00	1.00
5-7 days	1014 (650, 1547)	1330 (1216)	**2.16 (1.91, 2.42)**	**1.85 (1.63, 2.06)**
8+ days	619 (451, 879)	762 (503)	**1.42 (1.26, 1.57)**	**1.37 (1.22, 1.52)**
Trend			**P < 0.001**	**P < 0.001**

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.
¶ Severity of impairment assessed on the National Institutes of Health Stroke Scale (NIHSS).
# Severity of disability assessed on the modified Rankin Scale (mRS).
Figures in bold in table indicate that the risk ratios is statiscally significant at the 95% confidence level.

5.5. Discussion

This is the first published study of the hospitalisation costs of stroke in Viet Nam. Our principal findings are that average total costs per stroke admission were USD 963 comprising USD560 for direct medical cost, USD 171 for direct non-medical cost, and USD 240 for indirect costs. Severity of impairment and LOS were predictors of all cost categories and each was greater for patients with ICH (but not independently of severity and LOS). Wealthier patients had higher average direct medical costs and indirect cost, and total cost. Patients with comorbidity incurred higher direct medical costs.

The mean LOS of 6.6 days (5.9 days for IS and 8.7 days for ICH) was less than the range (9-35 days) in a European comparison [326] and was also less than estimates of 17 days and 13.9 days reported for Singapore [274] and Korea [275] respectively. Consistent with the findings of Mamoli et al. [333], type and severity of stroke contributed independently to LOS but the proportion of patients at this hospital with each major stroke type was similar to published results [12,18,19,21] for other LMICs whilst the proportion with severe disability at admission was higher [334]. The stroke unit in this study had 130 beds at the time of this study, but the average number of patients requiring treatment was greater than 140 per day (unpublished annual report of hospital).Our shorter LOS could be due to the overload of stroke patients and the pressure this places for early discharge once patients have overcome the acute phase and started to recover. It could also be due to patients and their families not being able to afford the direct medical costs, although a majority of participants asked a relative to cover the costs related to stroke treatment during the hospitalisation.

Our findings were broadly consistent with findings of other studies on distribution of resource use in other Asian countries/LMICs such as Pakistan [262], Singapore [274], Korean [275] and Japan [276], with diagnostic imaging (32% of average costs), medications (26%) and bed-day fees (23%) the largest contributors to direct medical costs.

The average costs per discharge in 115 People's Hospital of USD 560 is relatively low compared to estimates for HICs and at the low end of the range for LMICs of USD 416 in Senegal to USD 8,424 in Nigeria [257]. This could be due to administrative charges – particularly the low salaries of hospital medical staff – not adequately reflecting the cost of resource use in Viet Nam. Economic costs are difficult to estimate in any setting, and problematic in countries such as Viet Nam where diagnosis-related group (DRG) classification systems and activity-based funding are yet to replace historic budgets. The hospital charges billed to patients was the only source of cost data that was available to us.

Our study provided novel and important data on indirect costs of stroke incurred by patients and their caregivers. The indirect costs were estimated by assessing the loss of income due to time absent from work (other than sick leave or annual leave) for patients and caregivers who were working and earning regular income before the stroke onset. Loss of income, including that of caregivers, contributed 13% of total cost. The burden of informal care in Viet Nam may be due to the overcrowding of patients in hospital and the limited number of nurses in the stroke unit, requiring family members to contribute to the care of patients [293]. If valued according to productivity lost (including household productivity) as well as accounting for lost leisure time rather than focussing on just loss of income of patients and their caregivers, our indirect costs could be much higher.

Similar to findings for HICs [335] and other LMICs [262,263,268-271], severity of stroke and LOS were independent predictors of direct medical costs. Direct medical costs were higher for ICH than for IS partly due to greater severity and longer LOS. These findings are similar to those of studies conducted in China [263] and Italy [251,277,278]. Unless risk factors for non-communicable disease – particularly high blood pressure, which is important in the pathogenesis of ICH – are controlled better in the future, the total costs of treating stroke in LMICs will increase due to elevated proportions of ICH.

The direct medical cost of insured patients was nearly one-tenth lower than that of non-insured patients after adjustment for age, sex, wealth, comorbidity, severity of impairment (NIHSS) and LOS. In particular, costs of diagnostic imaging and bed-day fees were significantly lower for insured patients than for uninsured patients. Out-of-pocket expenditure was around three-quarters of total direct treatment costs for all stroke patients, and nearly half of total direct treatment costs for insured patients. In contrast, hospital charges for stroke patients were associated positively with health insurance status in studies conducted in China [263,336], prompting concerns [336] about over-use of resources for insured patients. In Viet Nam, health insurance is mostly provided by government, and covers 50-100% of treatment costs depending on type of health insurance (voluntary or commitment) and the particular mix of medical resources used for treatment. We found that the health insurance co-payment for bed-day fees was only around 5%, possibly because the reimbursement is for a standard bed (fee 10,000 VND/day) in a large room (with 10 beds) and with limited facilities in the room. The mean bed-day fee for a bed in a "service room" with 1-4 beds and better facilities including air conditioner and private toilet (range 150,000–500,000 VND/day) or an ICU bed (200,000 VND/day) is 15–50 times higher.

The financial burden of stroke on the families of patients with stroke and their caregivers is an important finding of our study. For a relatively high proportion of cases, stroke in Viet Nam occurs with severe impairment and disability, and these patients incur higher hospital costs for acute treatment and higher total costs overall. In addition, out-of-pocket expenditure is high due the incomplete population coverage of health insurance in Viet Nam – reportedly about 60% [283] but 54% in our study, compared to 62% in China [281] – and the limited co-payments received by insured persons. Despite reimbursement from health insurance, insured patients paid nearly half of direct treatment cost of stroke in the hospital. In this study, median direct medical costs and total costs of stroke were respectively 1.33 and 2.38 times higher than the median household income of respondents in this study (2,000,000 VND). The median direct medical costs and total costs of stroke were respectively 0.81 and 1.95 times higher for an insured patient, and 1.86 and 2.92 times higher for non-insured persons. These ratios would be 41% higher had they been calculated relative to the mean income per capita (3,399,000 VND) in Ho Chi Minh City in 2012. The out-of-pocket costs were similar to those reported by Kaur et al. [257] for LMICs. Three quarters of our patients relied on financial support from a relative to cover out-of-pocket costs, and almost one-in eleven had taken out a loan and 1% had sold household assets. In north-west India, 11% of stroke patients in 2012 had taken a loan to pay for treatment for stroke [269].

The 115 People's Hospital is a tertiary public hospital in Ho Chi Minh City where treatment of cerebral vascular disorders, such as stroke, is one of the treatment foci of the hospital. It is located in District 10, one of central business districts of Ho Chi Minh City and an area of relative affluence. Patients are referred to it from all areas of the city, but the stroke patients in our study had a higher median household income per adult than that of the general population of Ho Chi Minh City. In addition, the 25-64 year olds among them were less well educated

than their counterparts in the general population. This was not unexpected because studies in Viet Nam have shown that people with lower education are more likely to be tobacco smokers [73] and to have been diagnosed with high blood pressure and diabetes [337,338], which are important risk factors for stroke in Viet Nam [339].

The stroke unit in this hospital is one of leading stroke units in public hospitals in Ho Chi Minh City with a high standard of diagnostic imaging techniques and adherence to intensive stroke treatment guidelines. We assume that the direct medical costs of stroke treatment in our study would be broadly similar to treatment costs in other leading stroke units in the country, but higher than treatment costs in general departments in other public hospitals without a specialist stroke unit. With this caveat, our estimates of costs of stroke should provide a reliable, evidence-based guide for public health practitioners and health policy-makers in Viet Nam.

Our study has several strengths. First, we calculated the costs of stroke from a societal perspective. Our costs included direct medical costs and also non-medical costs and loss of income that are rarely reported in other studies due to procedural complexities in data collection. Most cost-of-illness studies have reported direct medical costs sourced from hospital administrative systems. Our findings provide a fuller and broader account of the costs of stroke in Viet Nam. Second, we conducted a prospective cohort study collecting clinical information from a treating neurologist, direct medical costs from the hospital administrative system, and non-medical costs and out-of-pocket expenses of patients and their caregivers as they occurred. There was less reliance on recall by patients or caregivers than would have occurred in a retrospective study, Third, rather than using possibly non-representative data on income and expenditure of the general population published by the General Statistics Office in Ho Chi Minh City, we collected information on the actual income and expenditure of a well-ascertained sample of our patient population to estimate the costs of stroke treatment. That this sample was recruited with high response proportions and minimal drop-out is a further strength.

However, our study has some limitations. First, all information on income and expenditure was collected by self-report of patients and their caregivers. The summary values appeared plausible in comparison with published data for the general population, but it might be subject to bias. Second, the direct medical costs used in this study are sourced from administrative charges that are influenced by government policy in respect of subsidisation of hospital treatment, and may not reflect adequately the true economic costs of treatment. Last, our findings on treatment costs extrapolate to major public hospitals with sophisticated stroke units. In addition, the non-medical costs and loss of income calculated in this study may not be representative of all stroke patients because our stroke patients had high incomes relative to the general population.

5.6. Conclusion

For the first time we present comprehensive estimates of the costs of hospital care for stroke in Viet Nam. Severity of stroke, LOS and household wealth were the major predictors of cost. Despite relatively short average LOS, the average out-of-pocket expenditure on direct medical costs was in the middle range of estimates for LMICs. Total direct and indirect costs amounted to almost two times median annual income of insured patients, and almost 3 times that of non-insured patients.

5.7. Postscript

This chapter has presented findings on the economic aspect of the burden of stroke including direct (medical and non-medical) and indirect costs during the hospitalisation. Severity of stroke, haemorrhagic stroke, LOS in hospital and the affluence of patient's families are found to be factors related to costs of stroke during hospitalisation. A chapter that follows (Chapter 7) reports on a study of the patient-centred outcome of HRQoL. There were not any tested HRQoL instruments available for use in stroke patients in Viet Nam at the time that study was conducted, however, and that made it necessary to assess the reliability and validity of the instrument selected. That instrument was the Duke Health Profile (DHP). The next chapter (Chapter 6) reports an assessment of the DHP for use with stroke patients or their caregivers.

Appendix 5: Additional findings on costs of stroke

Table A5.1: Characteristics of a cohort of patients with first-ever stroke in Ho Chi Minh City, Viet Nam, on discharge from hospital. [*]

	Men (N=229)	Women (N=208)
Ethnicity [†]		
Vietnamese	91.7% (210)	91.5% (190)
Chinese	8.3% (19)	8.7% (18)
Marital status [†]		
Married	89.1% (204)	55.9% (115)
Single	5.2% (12)	6.2% (13)
Divorced	2.2% (5)	1.9% (4)
Widower/widow	3.5% (8)	36.0% (76)
Living with spouse [†]		
Yes	76.7% (173)	36.6% (75)
No – living with children	17.6% (40)	56.1% (115)
No – living with others	5.7% (13)	7.3% (15)
Wealth index [†]		
1st quarter (richest)	27.4% (61)	22.3% (46)
2nd quarter	21.5% (48)	21.4% (44)
3rd quarter	27.8% (62)	24.3% (50)
4th quarter (poorest)	23.3% (52)	32.0% (66)
BMI [†]		
Mean (SD[‡])	22.8 (3.2)	22.9 (4.0)
Underweight (BMI< 18.5)	9.6% (22)	13.0% (27)
Normal ($18.5 \leq$ BMI < 23.0)	42.4% (97)	39.1% (81)
Overweight ($23.0 \leq$ BMI < 27.5)	39.7% (91)	37.2% (77)
Obese (BMI≥ 27.5)	8.3% (19)	10.6% (22)
Comorbidity [†]		
No	74.3% (170)	67.3% (140)
1 comorbidity	18.3% (42)	23.6% (49)
2+ comorbidities	7.4% (17)	9.1% (19)
Pre-disability [†]		
Yes	4.8% (11)	9.6% (20)
No	95.2% (219)	90.4% (191)

[*] The cohort consisted of 450 patients, 9 of whom died in-hospital prior to commencement of follow-up and 4 of whom had incomplete hospital cost data. This information is provided for the 437 patients alive at discharge with complete hospital cost data.

[†] Patient self-report.

[‡] SD = standard deviation

Table A5.2: Comparison of members of the cohort of stroke patients from 115 People's Hospital in Ho Chi Minh City with the general population.

	Stroke patients	General population
All persons[*]		
Monthly average income per person †		
Median (IQR[‡])	2,000,000 (1,560,000)	
Mean (SD[§])	2,641,000 (2,179,000)	3,399,000
1st fifth of distribution	891,000 (290,000)	1,230,000
2nd fifth of distribution	1,544,000 (134,000)	1,960,000
3rd fifth of distribution	2,092,000 (160,000)	2,599,000
4th fifth of distribution	2,892,000 (300,000)	3,470,000
5th fifth of distribution	5,911,000 (2,946,000)	7,717,000
Average number of person per household	4.1	3.8
Average monthly expenditure/person †		
Median (IQR[‡])	1,500,000 (1,000,000)	
Mean (SD[§])	1,708,000 (1,076,000)	2,363,000
1st fifth of distribution	709,000 (164,000)	1,209,000
2nd fifth of distribution	1,110,000 (105,000)	1,780,000
3rd fifth of distribution	1,480,000 (110,000)	2,115,000
4th fifth of distribution	1,963,000 (159,000)	2,512,000
5th fifth of distribution	3,328,000 (1,276,000)	4,165,000
Household assets: percentage with		
Telephone	97.7% (422/432)	93.4%
Television	99.8% (431/432)	94.3%
VCD/DVD player	87.2% (375/430)	57.0%
Air conditioner	26.5% (114/430)	23.2%
Refrigerator	90.0% (387/431)	66.1%
Hot water system	26.9% (116/431)	21.2%
Computer	47.6% (205/431)	41.9%
Motor cycle	94.2% (407/432)	93.9%
Car	3.5% (15/432)	2.7%
Education		
<Primary school	32.3% (141/437)	12.1%
Primary school	25.6% (112/437)	21.5%
Secondary school	19.2% (84/437)	28.1%
Higher secondary	14.9% (65/437)	25.0%
College/university	8.0% (35/437)	13.3%

	Stroke patients	General population
Persons aged 25–64 years [¶]		
Monthly income per person[#] [†]		
Median (IQR[‡])	2,062,000 (1,805,000)	1,400,000 (1,500,000)
Mean (SD[§])	2,715,000 (2,359,000)	1,791,000 (1,590,000)
1st fifth of distribution	849,000 (318,000)	470,000 (211,000)
2nd fifth of distribution	1,525,000 (126,000)	987,000 (88,000)
3rd fifth of distribution	2,089,000 (163,000)	1,492,000 (1,591,000)
4th fifth of distribution	2,880,000 (303,000)	2,187,000 (238,000)
5th fifth of distribution	6,060,000 (3,107,000)	4,355,000 (1,945,000)
Average number of person[#] per household	4.1 (2.5)	3.4 (1.8)
Education		
<Primary school	21.2% (52/245)	15.9% (257/1615)
Primary school	24.5% (60/245)	21.1% (341/1615)
Secondary school	25.3% (62/245)	22.4% (361/1615)
Higher secondary	19.2% (47/245)	24.7% (398/1615)
College/university	9.8% (24/245)	16.0% (258/1615)
Education (males)		
<Primary school	14.8% (22/149)	11.1% (80/725)
Primary school	19.5% (29/149)	20.2% (146/725)
Secondary school	26.5% (38149)	22.4% (163/725)
Higher secondary	26.2% (39/149)	27.1% (196/725)
College/university	14.2% (21/149)	19.2% (140/725)
Education (females)		
<Primary school	31.3% (30/96)	23.4% (208/890)
Primary school	32.3% (31/96)	22.5% (200/890)
Secondary school	25.0% (24/96)	22.3% (198/890)
Higher secondary	8.3% (8/96)	20.9% (186/890)
College/university	3.1% (3/96)	11.0% (98/890)

[*] Data for the Ho Chi Minh City general population taken from the report from General Statistics Office of Ho Chi Minh City, Viet Nam for the year 2012. For these comparisons, the general population data have not been weighted to age, sex and urban/rural distribution of the cohort of generally older stroke patients.

[†] Expressed in Viet Nam Dong (VND).

[‡] IQR = interquartile range, expressed as 75th percentile less 25th percentile of the distribution.

[§] SD = standard deviation.

[¶] Data for the Ho Chi Minh City general population taken from the Viet Nam STEPS Survey 2009–10 (Bui et al, 2015) and re-weighted to the age, sex and urban/rural distribution of the cohort of stroke patients.

[#] Number of persons per household includes children less than 18 years old of age living in the households of stroke patients, but is restricted to adults 18 years or older in the general population taken from the Viet Nam STEPS Survey 2009–10.

Table A5.3: Direct medical costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with other putative explanatory factors.

	LOS (days)	Mean costs (USD) and ratios of means			
	Mean (SD)	Median (IQR)	Mean (SD)	Ratio (95% CI)*	Ratio (95% CI)†
Disability before stroke					
No	4.3 (6.5)	386 (282, 562)	555 (564)	1.00	1.00
Yes	6.7 (3.0)	397 (287, 636)	623 (554)	1.05 (0.83, 1.27)	1.02 (0.85, 1.20)
Smoking					
No	6.7 (4.3)	391 (287, 590)	586 (590)	1.00	1.00
Yes	6.3 (4.0)	377 (270, 536)	501 (493)	0.91 (0.78, 1.04)	0.96 (0.85, 1.07)
Alcohol consumption					
No	6.6 (4.2)	387 (287, 578)	579 (561)	1.0	1.00
Yes	6.5 (4.3)	383 (266, 541)	535 (566)	0.89 (0.73, 1.05)	0.94 (0.79, 1.08)
High blood pressure					
No	6.6 (4.2)	383 (270, 541)	547 (549)	1.00	1.00
Yes	6.5 (4.3)	387 (287, 578)	574 (578)	1.03 (0.92, 1.14)	1.03 (0.94, 1.13)
BMI					
Underweight (BMI< 18.5)	7.0 (4.3)	324 (258, 599)	613 (707)	1.0	1.00
Normal (18.5≤ BMI ≤ 22.9)	6.5 (4.2)	368 (268, 565)	537 (556)	1.05 (0.88, 1.23)	1.13 (0.97, 1.28)
Overweight(23.0 ≤BMI≤ 27.4)	6.4 (4.0)	389 (289, 561)	548 (457)	1.13 (0.94, 1.32)	**1.23 (1.05, 1.40)**
Obese (BMI≥ 27.5)	7.0 (5.1)	464 (306, 569)	653 (772)	1.27 (0.97, 1.57)	1.31 (1.06, 1.57)
Trend				**P= 0.03**	**P= 0.003**

* Ratio of means (95% confidence interval) adjusted for age and sex.

† Ratio of means (95% confidence interval) adjusted for age, sex, severity of impairment.

Table A5.4. Distribution of medical resource use by severity of impairment of stroke.

	NIHSS≤ 7 (N=232)				NIHSS> 7 (N=187)				Ratio of means	
	mean	(SD)	median	(IQR)	mean	(SD)	median	(IQR)	ratio	95%CI
Consultant fees	1.4	(1.4)	1.5	(0.3, 1.5)	1.3	(0.8)	1.5	(0.3, 1.5)	1.06	(0.87, 1.24)
Bed-day fees	95.9	(81.2)	77.6	(62.1, 108.7)	166.5	(143.8)	124.3	(77.6, 186.4)	**1.58**	**(1.39, 1.77)**
Lab tests	53.5	(20.6)	50.3	(44.8, 54.2)	63.9	(35.5)	54.4	(47.9, 67.7)	**1.14**	**(1.07, 1.21)**
Diagnostic imaging	171.8	(96.3)	133	(117, 221)	190.7	(105.8)	148.6	(126.5, 248.1)	1.10	(0.98, 1.23)
Rehabilitation*	3.0	(18.1)	0	(0,0)	45.7	(214.4)	6.3	(0, 18.4)	**26.97**	**(9.90, 44.03)**
Medications	48.5	(134.3)	18.8	(12.2, 30.0)	276.7	(485.2)	52.6	(24.2, 302.2)	**3.43**	**(2.53, 4.32)**
Medical consumables	3.1	(6.6)	0.6	(0, 3.0)	14.1	(19.9)	8.7	(3.0, 18.6)	**17.05**	**(8.15, 25.94)**
Meals and feeding†	0.31	(2.7)	0	(0, 0)	2.2	(11.0)	0	(0,0)	4.69	(-4.02, 13.41)
Other	11.4	(7.1)	9.6	(7.5, 12.5)	20.1	(13.0)	16.7	(11.7, 25.0)	**1.65**	**(1.49, 1.81)**
Total	390.9	(256.3)	308.0	(263.4, 452.7)	786.3	(754.0)	506.8	(346.4, 941.1)		

* includes physiotherapy and costs of minor surgical procedure

† included special diet and feeding

Table A5.5. Distribution of medical resource use by length of stay (LOS).

	LOS< 6 (N=218)				LOS≥ 6 (N=219)				Ratio of means	
	mean	(SD)	median	(IQR)	mean	(SD)	median	(IQR)	diff	95% CI
Consultant fees	1.4	(1.4)	1.6	(0.3, 1.6)	1.3	(0.8)	1.6	(0.3, 1.6)	0.93	(0.78, 1.09)
Bed-day fees	68.8	(37.4)	62.2	(46.6, 77.7)	185.4	(139.1)	134.6	(108.8, 207.2)	**2.38**	**(2.16, 2.61)**
Lab tests	52.4	(16.2)	50.3	(44.7, 54.4)	63.6	(36.0)	53.2	(47.3, 65.5)	**1.13**	**(1.06, 1.20)**
Diagnostic imaging	164.3	(90.7)	133.1	(116.2, 193.9)	192.6	(107.0)	148.7	(126.9, 247.1)	**1.16**	**(1.03, 1.29)**
Rehabilitation*	21.9	(182.8)	0	(0,0)	21.6	(84.9)	5.2	(0, 15.5)	**10.05**	**(4.08, 16.03)**
Medications	70.2	(206.4)	16.0	(10.4, 24.2)	223.8	(438.4)	47.3	(27.2, 138.0)	**3.65**	**(2.77, 4.54)**
Medical consumables	3.8	(7.7)	0.9	(0, 4.4)	12.5	(18.9)	8.3	(0.8, 15.8)	**7.94**	**(3.64, 12.24)**
Meals and feeding†	0.3	(2.6)	0	(0,0)	2.1	(10.5)	0	(0,0)	4.09	(-3.39, 11.59)
Other	9.2	(3.1)	8.7	(7.1, 10.4)	21.5	(12.5)	18.5	(13.2, 26.8)	**2.08**	**(1.93, 2.24)**
Total	392.6	(382.5)	286.8	(251.2, 413.0)	727.2	(657.2)	522.3	(378.0, 851.6)		

* includes physiotherapy and costs of minor surgical procedure

† included special diet and feeding

Table A5.6: Average direct non-medical costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with putative explanatory factors.

			Mean costs and ratio of means (N=437)					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
All patient	104	(64, 168)	168	(482)				
Sex								
Male	103	(62, 154)	175	(626)	1.00		1.00	
Female	106	(68, 171)	161	(241)	1.13	(0.91, 1.36)	1.10	(0.90, 1.31)
Age group								
< 45 years	98	(63, 173)	147	(161)	1.00		1.00	
45-54 years	93	(67, 150)	223	(949)	1.00	(0.62, 1.37)	1.12	(0.72, 1.52)
55-64 years	95	(51, 146)	119	(106)	0.74	(0.46, 1.02)	0.90	(0.58, 1.22)
65-74 years	114	(66, 191)	166	(179)	1.00	(0.62, 1.38)	1.04	(0.66, 1.42)
75+ years	115	(74, 201)	179	(301)	1.07	(0.67, 1.47)	1.05	(0.67, 1.43)
P value					P=0.52		P=0.99	
Wealth index								
4th quarter (richest)	114	(63, 199)	149	(128)	1.00		1.00	
3rd quarter	100	(67, 206)	262	(981)	1.13	(0.80, 1.46)	1.22	(0.89, 1.56)
2nd quarter	105	(65, 162)	167	(297)	1.03	(0.74, 1.31)	1.07	(0.79, 1.35)
1st quarter (poorest)	98	(61, 145)	114	(89)	0.85	(0.61, 1.09)	0.91	(0.67, 1.15)
P value					P=0.18		P=0.32	
Health insurance								
No	98	(65, 153)	183	(666)	1.00		1.00	
Yes	109	(63, 171)	156	(228)	0.98	(0.77, 1.18)	0.98	(0.79, 1.17)

	Median	IQR	Mean costs and ratio of means (N=437) Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Comorbidity								
No comorbidity	104	(65, 160)	179	(566)	1.00		1.00	
1 comorbidity	94	(52, 159)	131	(138)	0.85	(0.63, 1.06)	0.86	(0.65, 1.06)
2-6 comorbidities	151	(89,233)	174	(116)	1.14	(0.73, 1.54)	0.94	(0.61, 1.26)
P value					P=0.91		P=0.33	
Type of stroke								
IS	96	(62, 152)	126	(112)	1.0		1.00	
ICH	135	(83, 254)	302	(954)	**1.60**	**(1.25, 1.95)**	1.19	(0.90, 1.47)
Severity of impairment¶								
Not severe (NIHSS ≤ 7)	90	(61, 129)	148	(618)	1.0		1.00	
Severe (NIHSS > 7)	135	(74, 229)	188	(253)	**1.50**	**(1.21, 1.80)**	**1.25**	**(1.00, 1.49)**
Severity of disability#								
Least severe (mRS 0/1)	87	(63, 105)	83	(43)	1.00		1.00	
Intermediate (mRS 2/3)	94	(61, 148)	174	(720)	**1.36**	**(0.89, 1.86)**	1.24	(0.83, 1.66)
Most severe (mRS 4/5)	121	(74, 211)	183	(249)	**1.74**	**(1.13, 2.36)**	1.24	(0.78, 1.70)
P value					P=0.002		P=0.38	
Length of stay								
0-4 days	77	(47, 108)	88	(80)	1.00		1.00	
5-7 days	155	(92, 284)	277	(773)	**2.44**	**(1.89, 2.99)**	**2.09**	**(1.59, 2.58)**
8+ days	107	(68, 152)	125	(91)	**1.50**	**(1.13, 1.87)**	**1.38**	**(1.04, 1.72)**
P value					P=0.002		P=0.002	

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.
¶ Severity of impairment assessed on the National Institutes of health Stroke Scale (NIHSS).
# Severity of disability assessed on the modified Rankin Scale (mRS).

Table A5.7: Direct non-medical costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with other putative explanatory factors.

			Mean costs and ratio of means					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Disability before stroke								
No	106	(65, 168)	171	(503)	1.00		1.00	
Yes	114	(80, 205)	170	(135)	1.22	(0.82, 1.61)	1.22	(0.86, 1.57)
Smoking								
No	104	(67, 171)	188	(577)	1.00		1.00	
Yes	109	(66, 157)	133	(107)	0.96	(0.75, 1.17)	1.02	(0.82, 1.22)
Alcohol consumption								
No	104	(68, 172)	160	(226)	1.00		1.00	
Yes	109	(62, 154)	188	(703)	0.93	(0.67, 1.20)	1.02	(0.76, 1.29)
High blood pressure								
No	104	(63, 160)	192	(661)	1.00		1.00	
Yes	108	(71, 170)	148	(132)	1.03	(0.86, 1.20)	1.06	(0.90, 1.22)
BMI								
Underweight (BMI < 18.5)	118	(78, 181)	152	(126)	1.00		1.00	
Normal ($18.5 \leq$ BMI ≤ 22.9)	107	(66, 172)	218	(748)	0.95	(0.68, 1.21)	1.02	(0.76, 1.28)
Overweight($23.0 \leq$ BMI≤ 27.4)	100	(62, 161)	137	(123)	0.89	(0.64, 1.14)	0.97	(0.72, 1.22)
Obese (BMI≥ 27.5)	100	(77, 162)	139	(111)	0.97	(0.62, 1.33)	0.97	(0.64, 1.30)
Trend					P=	0.61	P=	0.62

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.

Table A5.8: Average direct non-medical costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with other putative explanatory factors.

			Mean costs and ratio of means					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Disability before stroke								
No	104	(63, 165)	169	(499)	1.00		1.00	
Yes	113	(78, 205)	165	(137)	1.12	(0.69, 1.54)	1.15	(0.73, 1.56)
Smoking								
No	103	(65, 170)	185	(572)	1.00		1.00	
Yes	109	(63, 154)	131	(107)	0.99	(0.72, 1.25)	1.09	(0.81, 1.36)
Alcohol consumption								
No	104	(68, 172)	158	(225)	1.00		1.00	
Yes	107	(61, 150)	182	(692)	0.85	(0.57, 1.14)	0.97	(0.66, 1.29)
High blood pressure								
No	103	(62, 159)	191	(658)	1.00		1.00	
Yes	107	(66, 170)	144	(132)	0.92	(0.73, 1.11)	0.97	(0.78, 1.15)
BMI								
Underweight (BMI< 18.5)	108	(76, 178)	145	(127)	1.00		1.00	
Normal ($18.5 \leq$ BMI$\leq$ 22.9)	106	(63, 170)	213	(740)	1.07	(0.71, 1.43)	1.18	(0.80, 1.56)
Overweight($23.0 \leq$ BMI $\leq$27.4)	100	(62, 161)	136	(123)	1.03	(0.67, 1.38)	1.10	(0.74, 1.46)
Obese (BMI $\geq$ 27.5)	96	(77, 145)	136	(112)	1.02	(0.56, 1.48)	0.93	(0.52, 1.33)
Trend					P=	0.90	P=	0.56

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.

Table A5.9: Average indirect costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with putative explanatory factors.

			Mean costs and ratios of means					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
All patient	62	(0, 186)	172	(349)				
Sex								
Male	62	(0, 166)	187	(401)	1.00		1.00	
Female	62	(0, 186)	156	(280)	1.47	(0.66, 2.29)	1.23	(0.55, 1.90)
Age group								
<45 years	124	(62, 249)	243	(367)	1.00		1.00	
45-54 years	120	(36, 186)	204	(415)	0.56	(0.06, 1.06)	0.60	(0.07, 1.12)
55-64 years	55	(0, 186)	189	(405)	**0.29**	**(0.03, 0.55)**	**0.37**	**(0.04, 0.70)**
65-74 years	21	(0, 141)	118	(199)	0.09	(0, 0.18)	0.10	(0, 0.21)
75+ years	29	(0, 155)	141	(308)	0.13	(0, 0.26)	0.12	(0, 0.25)
Trend					P<	0.001	P<	0.001
Wealth index								
4th quarter (richest)	62	(0, 259)	251	(477)	1.00		1.00	
3rd quarter	85	(19, 224)	219	(397)	1.55	(0.34, 2.76)	1.89	(0.44, 3.33)
2nd quarter	67	(9, 168)	126	(164)	1.01	(0.23, 1.79)	1.05	(0.26, 1.85)
1st quarter (poorest)	43	(0, 140)	113	(291)	**0.55**	**(0.11, 0.98)**	0.63	(0.13, 1.12)
Trend					P=	0.06	P=	0.09
Health insurance								
No	62	(0, 155)	166	(375)	1.00		1.00	
Yes	62	(0, 197)	177	(325)	1.45	(0.61, 2.30)	1.37	(0.59, 2.15)

	Median	IQR	Mean costs and ratios of means					
			Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Comorbidity								
No comorbidity	73	(0, 186)	193	(394)	1.00		1.00	
1 comorbidity	41	(0, 160)	114	(167)	**0.53**	**(0.14, 0.92)**	**0.44**	**(0.11, 0.77)**
2-6 comorbidities	56	(0, 171)	141	(249)	0.56	(0, 1.17)	**0.45**	**(0, 0.94)**
Trend					P=	0.05	P=	0.007
Type of stroke								
IS	58	(0, 155)	155	(322)	1.00		1.00	
ICH	93	(8, 225)	227	(419)	1.43	(0.51, 2.35)	1.05	(0.29, 1.81)
Severity of impairment¶								
Not severe (NIHSS ≤ 7)	50	(0, 140)	131	(287)	1.00		1.00	
Severe (NIHSS > 7)	86	(0, 228)	224	(416)	1.94	(0.86, 3.02)	1.70	(0.72, 2.69)
Severity of disability#								
Least severe (mRS 0/1)	38	(0, 128)	97	(154)	1.00		1.00	
Intermediate (mRS 2/3)	62	(5, 150)	158	(367)	2.55	(0, 5.33)	1.76	(0.01, 3.51)
Most severe (mRS 4/5)	86	(0, 212)	202	(366)	3.77	(0, 7.76)	1.58	(0, 3.34)
Trend					P=	0.05	P=	0.60
Length of stay								
0-4 days	41	(0, 120)	104	(235)	1.00		1.00	
5-7 days	83	(0, 259)	245	(475)	2.45	(0.79, 4.11)	1.61	(0.48, 2.73)
8+ days	88	(19, 188)	158	(236)	2.42	(0.69, 4.16)	1.95	(0.59, 3.31)
Trend					P=	0.05	P=	0.11

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.
¶ Severity of impairment assessed on the National Institutes of Health Stroke Scale (NIHSS).
# Severity of disability assessed on the modified Rankin Scale (mRS).
Figures in bold in table indicate that the risk ratios is statiscally significant at the 95% confidence level

Table A5.10: Indirect costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with other putative explanatory factors.

			Mean costs and ratio of means					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Disability before stroke								
No	124	(56, 249)	242	(392)	1.00		1.00	
Yes	82	(21, 155)	222	(402)	0.71	(0.31, 1.11)	0.81	(0.37, 1.24)
Smoking								
No	108	(41.4, 233.0)	216	(319)	1.00		1.00	
Yes	136	(70.3, 343.7)	295	(512)	1.47	(0.93, 2.02)	1.57	(1.02, 2.12)
Alcohol consumption								
No	120	(48, 254)	229	(322)	1.00		1.00	
Yes	124	(62, 230)	256	(472)	0.87	(0.44, 1.29)	0.83	(0.45, 1.22)
High blood pressure								
No	130	(62, 249)	264	(461)	1.00		1.00	
Yes	93	(50, 249)	216	(289)	0.93	(0.67, 1.19)	0.94	(0.69, 1.18)
BMI								
Underweight (BMI < 18.5)	103	(51, 311)	261	(378)	1.00		1.00	
Normal ($18.5 \leq$ BMI ≤ 22.9)	94	(41, 207)	205	(351)	0.77	(0.43, 1.11)	0.92	(0.53, 1.31)
Overweight($23.0 \leq$ BMI≤ 27.4)	136	(62, 346)	275	(408)	0.99	(0.54, 1.43)	1.10	(0.62, 1.58)
Obese (BMI≥ 27.5)	158	(93, 316)	235	(221)	1.15	(0.45, 1.84)	1.32	(0.53, 2.11)
Trend					P=	0.29	P=	0.20

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.

Table A5.11: Average indirect costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with other putative explanatory factors.

			Mean costs and ratio of means					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Disability before stroke								
No	67	(0, 186)	175	(350)	1.00		1.00	
Yes	17	(0, 93)	137	(331)	0.56	(0, 1.22)	0.57	(0, 1.25)
Smoking								
No	50	(0, 176)	149	(283)	1.00		1.00	
Yes	91	(17, 218)	227	(466)	2.46	(0.59, 4.34)	2.84	(0.74, 4.95)
Alcohol consumption								
No	62	(0, 190)	164	(292)	1.00		1.00	
Yes	65	(0, 155)	182	(414)	0.89	(0.04, 1.74)	0.91	(0.05, 1.76)
High blood pressure								
No	87	(10, 186)	197	(416)	1.00		1.00	
Yes	50	(0, 166)	145	(257)	0.63	(0.26, 1.00)	**0.62**	**(0.27, 0.98)**
BMI								
Underweight (BMI< 18.5)	62	(21, 176)	197	(347)	1.00		1.00	
Normal (18.5≤BMI≤ 22.9)	60	(0, 149)	149	(312)	0.55	(0.07, 1.03)	0.64	(0.08, 1.21)
Overweight (23.0≤ BMI≤ 27.4)	70	(0, 214)	194	(409)	**0.53**	**(0.05, 1.00)**	0.60	(0.06, 1.15)
Obese (BMI≥ 27.5)	93	(0, 186)	155	(211)	0.36	(0, 0.80)	0.38	(0, 0.87)
Trend					P=	0.11	P=	0.14

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.

Table A5.12: Average indirect costs (USD) of treatment of stroke patients at 115 People's Hospital, Ho Chi Minh City, and associations with other putative explanatory factors.

			Mean costs and ratio of means					
	Median	IQR	Mean	SD	Ratio	(95% CI)*	Ratio	(95% CI)†
Disability before stroke								
No	620	(424, 1013)	899	(904)	1.00		1.00	
Yes	595	(411, 807)	924	(903)	0.98	(0.76, 1.20)	0.97	(0.79, 1.14)
Smoking								
No	630	(419, 1028)	920	(952)	1.00		1.00	
Yes	610	(432, 953)	859	(780)	0.94	(0.80, 1.09)	1.02	(0.90, 1.15)
Alcohol consumption								
No	620	(417, 1029)	902	(821)	1.00		1.00	
Yes	617	(436, 974)	899	(1005)	0.90	(0.72, 1.08)	0.97	(0.81, 1.12)
High blood pressure								
No	611	(436, 1010)	936	(1049)	1.00		1.00	
Yes	639	(417, 1016)	863	(714)	0.99	(0.87, 1.10)	1.00	(0.90, 1.09)
BMI								
Underweight (BMI < 18.5)	570	(463, 1132)	955	(844)	1.00		1.00	
Normal (18.5≤ BMI≤ 22.9)	602	(411, 918)	900	(1101)	0.94	(0.76, 1.12)	1.03	(0.87, 1.19)
Overweight (23.0≤ BMI≤ 27.4)	640	(421, 1057)	878	(691)	1.00	(0.81, 1.20)	1.11	(0.93, 1.28)
Obese (BMI ≥ 27.5)	698	(541, 1223)	944	(810)	1.11	(0.82, 1.40)	1.13	(0.89, 1.37)
Trend					P=	0.25	P=	0.09

* Ratio of means (95%CI) adjusted for age, sex.
† Ratio of means (95%CI) adjusted for age, sex, severity of impairment and LOS.

Chapter 6: Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Viet Nam

6.1. Preface

Health-related quality of life (HRQoL) is one of outcomes following a stroke that was assessed at three months in the cohort study. However, there was not an instrument available that had been examined for reliability and validity in use with stroke patients in Viet Nam. This chapter presents findings of an assessment of the reliability and validity of the Duke Health Profile that was the instrument used to assess the HRQoL of stroke survivors three months after stroke in the cohort study. The text of this chapter is accepted for publication in the International Journal of Quality of Life Research [1]. The appendix is online supplementary data for the publication.

6.2. Introduction

HRQoL is an important patient-centred outcome following a stroke. There are several instruments designed to assess HRQoL. They include generic instruments (such as the Short Form 36, the Assessment of Quality of Life, the Sickness Impact Profile and the EuroQoL) and stroke-specific instruments (such as the Stroke Impact Scale and the Stroke Specific Quality of Life Scale). The Duke Health Profile (DHP) is a generic instrument that includes a wide range of dimensions not covered by some other instruments. It has been used for patients with cardiac failure [217], atrial fibrillation [218] and dementia [219]. For these reasons, and because the DHP had been translated and culturally adapted for use among adolescents in Viet Nam [212], and comparative data for the general adult population were available for this instrument [213], we selected it for measurement of HRQoL in a three-month follow-up study of stroke patients in Ho Chi Minh City, Viet Nam.

The problem in so doing was that the DHP had not been validated for use with stroke patients. Examination of the psychometric properties of an instrument when applied in novel circumstances is important. This prompted us to undertake a study of the reliability and validity of the DHP for use with stroke patients in Viet Nam. This would also provide novel information about the use of the DHP with stroke patients worldwide.

A possibly important issue was to ascertain whether proxy respondents could provide reliable information for patients who were cognitively impaired or otherwise in poor health. The DHP has not been validated for completion by a proxy respondent, and undertaking a validation study of proxy reports was also important as a precursor for monitoring the outcomes of stroke in Viet Nam and to provide information relevant for understanding the limitations of proxy responses to the DHP in other cultural settings.

The objectives of this study were to assess the reliability and validity of assessments of HRQoL from patient and proxy responses to the DHP. We did so in the advantageous circumstances of a follow-up study with near complete ascertainment and recruitment of stroke patients admitted with subsequent confirmation of diagnosis by neuroimaging to a major public hospital with a specialist stroke unit in Ho Chi Minh City, Viet Nam.

6.3. Methods

Subjects

This study was part of a cohort study of first-ever stroke patients (n=545) admitted to the Cerebrovascular Disease Department at 115 People's Hospital during the period 05/02/2012 to 15/09/2012. Stroke was diagnosed by neurologists using standard clinical criteria and brain imaging to confirm type (ischaemic or haemorrhagic) [3]. The cohort study was preceded by a pilot study from February 2012 to May 2012. The current sample was recruited from participants in the pilot and main studies. Inclusion criteria for stroke patients were (1) absence of cognitive impairment preventing communication with study personnel or comprehension of study requirements, (2) willingness to be contacted again after three months, and (3) willingness to have the DHP and EQ-5D instruments administered at that time and re-administered after 1 week. Inclusion criteria for caregivers were (1) being the daily caregiver of the stroke patient, and (2) willingness to provide responses to the DHP and the EQ-5D on behalf of the patient at the three-month contact and again one week later.

Data collection

Within the first 24 hours following admission, data were gathered on demographics and clinical presentation including stroke type and health status prior stroke. Severity of impairment following stroke was assessed by a neurologist using the National Institutes of Health Stroke Scale (NIHSS) [122] that grades severity according to clinical manifestations with scores ranging from 0 (no symptom) to 42 (very severe). Disability was assessed on the modified Rankin Scale (mRS) that grades functional impairments with scores ranging from 0 (no symptom) to 6 (death) [115]. At three months after stroke, patients and their proxies self-administered the DHP and a comparison instrument (EuroQoL EQ-5D), under the supervision of study staff (time 1). Instruments were re-administered 1 week later (time 2). Patients and proxies completed questionnaires separately when possible. The study staff responded to questions from participants, but provided pre-scripted answers where possible. Disability at three months was assessed using the mRS.

HRQoL Instruments

The DHP is a generic self-report instrument referenced to today or the last 7 days (full details are in the online supplement). In brief, there are six domains referring to health function (higher scores = better health): physical health, mental health, social health, general health, perceived health and self-esteem. Four domains refer to health dysfunction (higher scores = poorer health): anxiety, depression, pain and disability. With scoring reversed for those four domains, the scores on each domain range from 0 (poorest health) to 100 (best possible health). The DHP has previously been translated into the Vietnamese language (with accuracy of translation verified by back translation) [212].

The EQ-5D comprises 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (full details in online supplement). The EQ VAS records the respondent's self-rated health on a visual analogue scale with the endpoints labelled as "best imaginable health state" and "worst imaginable health state". The overall EQ-5D utility score (range: -0.263 [worst] to 1 [best]) was computed using weights for the South Korean general population [296] in the absence of a value set for Viet Nam.

Statistical Analysis

For each DHP dimension, mean scores were calculated over non-missing item scores and with stratification by study factors (sex, age, type of stroke, stroke severity at admission, disability at admission and at three months post stroke).

Absolute reliability was assessed by paired t-tests of the test-retest differences on each DHP and EQ-5D dimension and by calculating the standard error of measurement (SEM) and minimal detectable difference (MDD). Linear regression was used to assess whether differences in scores varied by study factors. Patterns of departure between test and retest values were assessed from Bland Altman plots. Relative reliability was estimated by the intra-class correlation coefficient (ICC). In this study an ICC value >0.81 was considered almost perfect agreement, 0.61-0.80 as substantial agreement, 0.41-0.60 as moderate agreement, 0.21-0.40 as fair agreement and 0.0-0.20 as slight agreement [307]. The same procedures were used to examine reliability of the proxy responses.

Convergent validity was assessed with an inter-instrument comparison by calculating rank correlations of the DHP dimension scores with EQ-5D component scores, utility score and EQ-VAS scores and with measures of impairment and disability. The rank correlation calculated for the EQ-5D individual components were not materially different to product moment correlations calculated with responses weighted using the South Korean value set (see **Table A6.3** in Appendix 6). Because the DHP dimensions are not independent, Monte-Carlo procedures were used to approximate the extract permutation distribution of the set of DHP dimensions with each EQ-5D score and with each measure of impairment and disability. The false discovery rate (FDR) for each dimension was calculated from the tails of the relevant permutation distribution. To control the FDR, the step-up procedure of Benjamini-Hochberg [340] under independent assumptions was applied to the permutation distributions. For comparison, without control for multiple comparisons, the correlations providing FDRs of 0.05, 0.01 and 0.005 in this sample size (n=108) are approximately 0.190, 0.247 and 0.312. Patterns of departure between the scores from each instrument were assessed by Bland Altman plots.

Ethics

All participants and their caregivers provided written consent. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee and ethics committees at Pham Ngoc Thach University of Medicine and 115 People's Hospital in Viet Nam.

6.4. Results

Characteristics of the 108 stroke patients are summarized in **Table 6.1**. They comprised 49.1% (53/108) females, with a mean age of 60.9 (SD 12.0) years. At admission, mean NIHSS was 7.7 (SD 0.6). Mean mRS was 3.3 (SD 0.1) at admission and 2.2 (SD 0.1) three months post-stroke. The 108 participants in the validation study were generally similar to the remaining 310 survivors at three months in the main study. The frequency of responses for each EQ-5D component, and the mean utility and VAS scores are presented in **Table A6.1** (see Appendix 6)

.

Table 6.1: Characteristics of stroke patients who participated in the validation study.

Characteristics	Male (N=55)		Female(N=53)	
Age : Mean (SD*)	59.4	(11.2)	62.4	(12.8)
Type of stroke				
Ischemic stroke	72.7%	(40/55)	66.0%	(35/53)
Intra-cerebral hemorrhage	27.3%	(15/55)	34.0%	(18/53)
Severity of impairment at admission				
Not severe stroke ($0 \leq$ NIHSS ≤ 7)	62.3%	(33/53)	56.0%	(28/50)
Severe stroke ($8 \leq$ NIHSS ≤ 42)	37.7%	(20/53)	44.0%	(22/50)
Severity of disability at admission				
Not severe (mRS ≤ 2)	25.0%	(13/52)	20.7%	(11/53)
Severe (mRS ≥ 3)	75.0%	(39/52)	79.3%	(42/53)
Severity of disability at 3month				
Not severe (mRS ≤ 2)	63.6%	(35/55)	58.5%	(31/55)
Severe (mRS ≥ 3)	36.4%	(20/55)	41.5%	(22/55)
The Duke Health Profile: Mean (SD*)				
Physical health	59.1	(26.2)	49.4	(25.4)
Mental health	65.3	(22.3)	64.5	(22.8)
Social health	56.9	(11.5)	58.5	(12.9)
General health	60.4	(15.1)	57.5	(15.5)
Perceived health	35.5	(34.3)	33.1	(35.3)
Self-esteem	75.8	(15.2)	75.8	(18.4)
Anxiety	73.3	(17.2)	72.5	(19.0)
Depression	68.7	(21.4)	64.2	(22.9)
Pain	63.6	(36.6)	59.4	(38.0)
Disability	68.2	(43.4)	75.5	(37.5)

*denotes standard deviation

Table 6.2 shows mean differences on retest after one week for DHP. Each difference is small relative to its SD, SEM and MDD, and generally less than 3 points. Most differences are positive showing that the time 2 scores generally were greater, and not consistently associated with age, type of stroke, NIHSS or mRS. Bland-Altman plots of difference against average did not reveal systematic patterns in the differences or greater than expected numbers of outlying values on multi-item components.

There were greater than expected numbers of outliers and large SDs (**Table 6.2**) for perceived health, pain and disability indicating changes in assessments had occurred. The ICCs ranged from 0.60 for social health, self-esteem and anxiety to 0.86 for disability. The test -retest results for the EQ-5D was similar to the DHP and is provided in the online supplement (**Table A6.4, Appendix 6**).

Table 6.2: Test and retest reliability of assessments of HRQoL made one week apart from patient responses to the DHP (n=108).

	Test		Re-test		Difference		Reliability index			
	Mean	**(SD*)**	**Mean**	**(SD*)**	**Mean**	**(SD*)**	**SEM†**	**MDD‡**	**ICC§**	**95% CI**
Physical health	54.4	(26.1)	54.8	(25.6)	0.6	(17.0)	12.0	33.2	0.78	(0.70, 0.85)
Mental health	64.9	(22.5)	67.5	(20.9)	2.6	(16.7)	11.9	33.0	0.70	(0.59, 0.78)
Social health	57.7	(12.2)	59.4	(13.3)	1.7	(11.4)	8.1	22.5	0.60	(0.46, 0.71)
General health	58.9	(15.3)	60.6	(16.3)	1.7	(11.0)	7.8	21.7	0.75	(0.66, 0.83)
Perceived health	34.3	(34.6)	35.2	(35.0)	0.9	(25.6)	18.0	49.9	0.73	(0.63, 0.81)
Self-esteem	75.8	(16.8)	78.1	(15.7)	2.3	(14.6)	10.4	28.8	0.60	(0.46, 0.70)
Anxiety	72.9	(18.0)	75.8	(18.6)	2.9	(16.2)	11.6	32.2	0.60	(0.47, 0.71)
Depression	66.5	(22.2)	69.1	(22.1)	2.6	(18.9)	13.4	37.1	0.64	(0.51, 0.74)
Anxiety-depression	71.6	(18.9)	74.1	(18.8)	2.4	(16.0)	11.4	31.5	0.64	(0.51, 0.73)
Pain	61.6	(37.2)	64.9	(34.5)	3.3	(30.9)	21.9	60.7	0.63	(0.50, 0.73)
Disability	71.8	(40.6)	73.1	(39.5)	1.4	(21.0)	14.8	41.1	0.86	(0.81, 0.90)

* denotes standard deviation,
† denotes denotes standard error of measurement,
‡ denotes minimal detectable difference,
§ denotes intra-class correlation coefficient

Table 6.3: Rank correlation of DHP dimensions with EQ-5D components, utility score and visual analogue scale (VAS) assessed from patient report and with measures of impairment and disability (n=108).

	Dimensions of Duke Health Profile										
	PH	**MH**	**SH**	**Per**	**SE**	**Anx**	**Dep**	**AD**	**Pain**	**Dis**	**GH**
EQ-5D											
Morbidity	-0.66***	-0.28**	-0.16	-0.32**	-0.22*	-0.25*	0.36***	-0.34***	-0.26*	-0.52***	-0.54***
Self-care	-0.55***	-0.27**	-0.19	-0.38***	-0.16	-0.18	-0.30**	-0.30**	-0.24*	-0.60***	-0.49***
Usual activities	-0.62***	-0.33**	-0.11	-0.38***	-0.16	-0.25*	-0.39***	-0.35***	-0.26*	-0.59***	-0.54***
Pain/Discomfort	-0.37***	-0.35***	-0.16	-0.24*	-0.29**	-0.33***	-0.36***	-0.38***	-0.65***	-0.30**	-0.45***
Anxiety/Depression	-0.28**	-0.62***	-0.17	-0.37***	-0.43***	-0.41***	-0.53***	-0.56***	-0.30**	-0.25**	-0.53***
Utility score	0.69***	0.46***	0.24*	0.43***	0.33**	0.35***	0.49***	0.48***	0.37***	0.63***	0.68***
VAS	0.55***	0.49***	0.17	0.47***	0.37***	0.48***	0.55***	0.55***	0.41***	0.49***	0.61***
NIHSS (impairment) **at admission**	-0.30**	-0.24*	-0.14	-0.17	-0.19	-0.12	-0.26*	-0.23*	-0.16	-0.16	-0.34**
mRS (disability) **at admission**	-0.32**	-0.18	-0.11	-0.34***	-0.16	-0.18	-0.25*	-0.20	-0.12	-0.25*	-0.30**
mRS (disability) **at 3 month**	-0.60***	-0.32***	-0.26**	-0.48***	-0.23*	0.27**	-0.32***	-0.34***	-0.25**	-0.61***	-0.56***

* denotes p<0.05
** denotes p<0.01
*** denotes p<0.001

Table 6.3 summarizes the associations of DHP dimensions with the EQ-5D components, utility score and VAS scores assessed from patients. The strongest association was between the DHP general health dimension and the EQ-5D utility score (r = 0.68), but its correlations with each of the EQ-5D components (range –0.45 to –0.54) were somewhat weaker. Otherwise the correlations are generally modest in size unless they measured similar constructs, such as between DHP physical health and EQ-5D components on physical function (morbidity r = –0.66, self-care r = –0.55, usual activities r = – 0.62); and between DHP mental health and EQ-5D anxiety/depression (r = –0.62). There were strong associations between mRS and DHP physical health (r = –0.60), disability (r = –0.61) and general health (r = –0.56) (**Table 6.3**).

The assessments of 94 patients were compared with those of a nominated proxy. The 91 proxies of known relationship to patients included 86% (78/91) who were next-of-kin (husband/wife/children/parents). Information is provided in **Table A6.2** (Appendix6). The assessments of patient HRQoL by the proxies were correlated with mRS and NIHSS of the patient on admission, and particularly with mRS at three months (DHP social health r = -0.16; DHP other than social health: r = –0.29 to r = –0.67).

Table 6.4 shows that mean differences between patient and proxy assessment were small relative to SDs, but indicate that the patient derived scores were greater than those from proxies. The differences were greatest for physical health (p = 0.067), social health (p = 0.005), general health (p <0.001), self-esteem (p = 0.015), anxiety (p= 0.01) and depression (p = 0.09).

The two dimensions with greatest variability were perceived health and pain. Male proxies tended to over-estimate the perceived health and pain of male patients but under-estimate the perceived health and pain of female patients. Female proxies tended to under-estimate the HRQoL of patients and particularly that of female patients. Of note is that other than the ICCs for mental health and perceived health, the ICCs for proxy-patient variation were generally similar to those for the patient test-retest. The proxy-patient differences were at most weakly associated with patient and proxy characteristics (**Table A6.3** in Appendix 6). The patient-proxy reliability for the EQ-5D was similar to the DHP and is provided in the online supplement (**Table A6.4** in Appendix 6).

Table 6.5 summarizes the associations of DHP dimensions with the EQ-5D components, utility score and VAS scores assessed from information provided by caregivers, and with measures of impairment and disability. The rank correlations were generally similar to, but slightly greater than, those assessed from patient reports (see **Table 6.3**).

Table 6.4: Patient-proxy reliability of measurements of HRQoL using the DHP.

	Patient (N=94)		Proxy (N=94)		Difference		Reliability index			
	Mean	(SD*)	Mean	(SD*)	Mean	(SD*)	SEM†	MDD‡	ICC§	95% CI
Physical health	53.7	(26.7)	50.9	(26.6)	-2.9	(15.0)	10.7	29.7	0.83	(0.75, 0.88)
Mental health	64.1	(22.4)	62.9	(22.1)	-1.2	(20.8)	14.6	40.6	0.55	(0.41, 0.67)
Social health	58.4	(12.2)	55.2	(12.0)	-3.2	(10.8)	7.9	21.9	0.57	(0.42, 0.69)
General health	59.1	(15.3)	54.8	(16.3)	-4.3	(10.4)	7.8	21.7	0.75	(0.62, 0.83)
Perceived health	31.4	(35.2)	28.7	(35.2)	-2.7	(29.7)	21.0	58.1	0.61	(0.48, 0.72)
Self-esteem	77.0	(15.9)	73.3	(16.5)	-3.7	(14.5)	10.5	29.1	0.59	(0.45, 0.70)
Anxiety	73.8	(16.4)	69.4	(18.3)	-4.3	(16.2)	11.8	32.6	0.57	(0.43, 0.69)
Depression	66.6	(21.5)	63.1	(24.5)	-3.5	(19.8)	14.1	39.1	0.62	(0.49, 0.72)
Anxiety-depression	72.0	(18.1)	67.9	(20.4)	-4.1	(15.4)	11.2	31.1	0.66	(0.54, 0.76)
Pain	61.2	(36.8)	58.5	(37.8)	-2.7	(28.7)	20.3	56.3	0.69	(0.58, 0.78)
Disability	69.6	(41.2)	70.7	(41.4)	1.1	(7.3)	5.2	14.4	0.98	(0.97, 0.99)

* denotes standard deviation, † denotes standard error of measurement, ‡ denotes minimal detectable difference, § denotes intra-class correlation coefficient

Table 6.5: Rank correlation of DHP dimensions with EQ-5D components, utility score and visual analogue scale (VAS) assessed from proxy reports and with measures of impairment and disability of the patients (n=94).

	Dimensions of Duke Health Profile										
	PH	**MH**	**SH**	**Per**	**SE**	**Anx**	**Dep**	**AD**	**Pain**	**Dis**	**GH**
EQ-5D											
Morbidity	-0.67***	-0.47*	-0.16	-0.34	-0.29	-0.41***	-0.49**	-0.50**	-0.48***	-0.67***	-0.63***
Self-care	-0.58***	-0.42***	-0.19	-0.13**	-0.28*	-0.42***	-0.46***	-0.45***	-0.42***	-0.56***	-0.59***
Usual activities	-0.65***	-0.31**	-0.14	-0.17	-0.23*	-0.38***	-0.40***	-0.40***	-0.42***	-0.64***	-0.55***
Pain/Discomfort	-0.56***	-0.42***	-0.08	-0.30**	-0.28**	-0.42***	-0.50***	-0.48***	-0.73***	-0.39***	-0.55***
Anxiety/Depression	-0.37***	-0.63***	-0.19	-0.48***	-0.47***	-0.47***	-0.54***	-0.57***	-0.38***	-0.33**	-0.57***
Utility score	0.74***	0.47***	0.17	0.28*	0.34**	0.50***	0.55***	0.55***	0.57***	0.64***	0.69***
VAS	0.62***	0.42***	0.16	0.32**	0.34**	0.41***	0.50***	0.50***	0.42***	0.48***	0.59***
NIHSS (impairment) **at admission**	-0.37**	-0.27*	-0.14	-0.22*	-0.22*	-0.27**	-0.31*	-0.31**	-0.34**	-0.23*	-0.37**
mRS (disability) **at admission**	-0.39**	-0.23*	-0.17	-0.24*	-0.20*	-0.29**	-0.38**	-0.32**	-0.28*	-0.33**	-0.37***
mRS (disability) **at 3 month**	-0.67***	-0.47***	-0.16	-0.34**	-0.29**	-0.41***	-0.49***	-0.50***	-0.48***	-0.67***	-0.63***

* denotes false discovery rate (FDR)<0.05, ** denotes FDR<0.01 and *** denotes FDR<0.005.

PH: physical health, MH: mental health, SH: social health, Per: perceived health, SE: self-esteem, Anx: anxiety, Dep: depression, AD: anxiety-depression, Dis: disability, GH: general health.

6.5. Discussion

This is the first study to assess the reliability and validity of the DHP for use in the field of stroke. The reliability of the DHP was moderate for assessments made by patients or by caregivers. When compared with scores on similar components of the EQ-5D, moderate convergent validity was found. The assessments of patient HRQoL by proxies were systematically lower than those by the patients themselves, but the patient-proxy differences were not clinically meaningful.

Attesting to their construct validity, HRQoL measured with the DHP was lower for women, decreased with age, and was lowest for patients with the most severe disability , consistent with findings in general population and adolescent samples in France [215,341] and Viet Nam [212,213]. Our findings, in respect of age, sex, stroke severity, and severity of disability were also consistent with studies of stroke survivors, but with HRQoL measured using SF-36 [248,342], Stroke-Specific Quality of Life [249], and the Stroke Impact Scale-16 [248].

We found patient test-retest differences were lower than various thresholds for determining clinically meaningful differences in measurements of HRQoL [343,344]. Despite this, scores were greater on second occasion for both HRQoL instruments, and mostly among male patients, suggesting that male patients upgraded assessments of HRQoL on the second occasion. The relative reliability of DHP for use with stroke patients was moderate to good. We were unable to find other studies of the reliability of DHP for use with stroke patients with which to compare our results. In addition, DHP dimensions of physical health, disability and general health were strongly correlated with severity of disability (mRS) at 3 month follow up (range -0.56 to -0.60). Our results comparing to EQ-5D are similar to those from a study of hospital patients aged 65-79 years old in France [345], showing moderate to good rank correlations between DHP and SF-36 dimensions of physical health (r = 0.59), mental health (r =0. 37) and general health (r = 0.56).

The patient-proxy differences generally fell below the values that could be considered to be clinically meaningful differences for HRQoL measurements [343,344]. We also found moderate ranking stability with a lowest ICC of 0.55. Generally, the patient-proxy ranking agreement appeared stronger for DHP dimensions involving physical than mental health, as might be expected. Our findings also revealed a tendency for women to provide lower assessments of HRQoL when reporting on behalf of stroke patients. Despite using other HRQoL instruments, other studies of proxy assessments of stroke patients HRQoL have produced similar findings. For example, using the Stroke Impact Scale, Duncan et al. [346] found moderate ICCs between patient and proxy assessments (0.50 to 0.83). Several other investigators have found that proxies report lower HRQoL scores than patients themselves [233,235,346,347]. This suggests that under reporting of HRQoL by proxies is not instrument-specific but rather a limitation of proxy assessment.

This study has several strengths. Firstly, our participants were recruited with high response (81.8% for patients and 87.0% for proxies) from the stroke unit of a major public hospital. Importantly, they were similar to the subjects in the larger cohort study. Secondly, information was gathered by trained local medical personnel, and using instruments culturally adapted for the Vietnamese population, and with minimal interference by staff. Thirdly, in addition to the assessment of reliability and validity of the patient-administered DHP, we also assessed this for proxy respondents.

Readers need to be aware of some possible limitations. Firstly, the DHP had only moderate reliability and validity in its original target USA population [198]. It was chosen because it retained its psychometric properties when used in other populations [345], and partly because it had already undergone translation and cultural adaption in Viet Nam [212]. Further, it includes dimensions of HRQoL, such as mental health, not covered by other translated instruments such as EQ-5D. Secondly, the weights for the South Korean general population were used to sum the responses to components of the EQ-5D. These weights may not reflect accurately the preferences of the Vietnamese population. Thirdly, because the DHP instrument requires recall of today or the previous week, it was necessary to re-test within a short time frame in order to limit the impact of real changes in the condition of the patient on the assessed stability of responses. Patients may have recalled their previous responses and, if so, this may influence their current responses. The time interval for previous studies of specific disease groups, such as dementia and stroke patients, has usually been short (around 2 weeks) [202,219,348]. Supporting our choice of one week, Marx et al. [349] found no clinically or statistically significant difference between the test-retest reliability of SF-36 for measurements of health status performed with a two-day interval and a two-week interval. Fourthly, though the interviewers separated patients from proxies during interviews, the confined living environment in Viet Nam sometimes meant that separation between some sets of respondents was limited. Finally, a limitation inherent to all validation of proxy assessments is that we cannot be sure of their validity for patients who actually require a proxy, such as those with cognitive impairment, severe aphasia or unconsciousness.

6.6. Conclusion

In conclusion, the DHP has moderate reliability and validity for use with stroke patients in Viet Nam including when it is necessary to obtain information from proxy respondents.

6.7. Postscript

Prior to using the DHP as a study instrument to assess HRQoL of stroke survivors from patient's self-report or from their caregivers as proxies, it was necessary to test the DHP for use with stroke patients. This chapter presented findings from a study of the reliability and validity of the DHP. In the next chapter, the findings of an assessment of the HRQoL of stroke survivors at three months and factors associate with poorer HRQoL are reported.

.

Appendix 6: Additional findings on examination on the reliability and validity of the EuroQoL (EQ-5D) and the DHP

Methods

HRQoL Instruments

The Duke Health Profile (DHP) is a generic health-related quality of life (HRQoL) instrument. It is a brief self-report instrument with good acceptability [198,214]. The DHP has 17 questions that form 10 domains. Six of the 10 domains refer to health function (higher scores indicate better health status): physical health (5 items), mental health (5 items), social health (5 items), general health (combining the 15 items used for the physical, mental and social health dimensions to indicate overall well-being), perceived health (single item) and self-esteem (5 of the items used for the mental and social health domains). The remaining four domains refer to health dysfunction (higher scores indicate poorer health status): anxiety (6 of the items used for general health), depression (5 of the items used for physical and mental health), pain (single item used for physical health) and disability (single item). Each question has 3 possible responses scored as 0, 1 or 2. Responses to the constituent items in each domain are added and the mean of the raw scores is normalized to lie on scale of 0 to 100. In reporting the results of this study, the scores for anxiety, depression, pain and disability were subtracted from 100 so the scale ranged from 0 (poorest health) to 100 (best possible health) for each of the 10 dimensions. Prior to use, the DHP was translated and back-translated. This version has previously been validated among healthy adolescents in Viet Nam [212].

The EQ-5D instrument is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal [220-222]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The version of the EQ-5D used in this study was the EQ-5D-3L. It contains the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system comprises 5 components: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each component has 3 response levels: no problems (0), some problems (1), and inability or extreme problems (2). The respondent is asked to indicate his/her health state by marking the box against the most appropriate statement in respect of each of the 5 components. The EQ VAS requires a respondent to record their self-rated health on a visual analogue scale with the endpoints labelled as “Best imaginable health state” and “Worst imaginable health state”.

Statistical Analysis

The ten dimensions of the DHP were coded and calculated according to the manual [214]. To calculate an EQ-5D utility score, the components were weighted and summed using weights for the South Korean general population [296] in the absence of a value set specific for the population of Viet Nam.

Inter-method comparisons were undertaken to assess convergent validity by calculating rank correlations between the DHP dimension scores and EQ-5D component scores, overall score or EQ-VAS scores. Patterns of departure between the scores from each instrument were assessed by visual inspection of Bland Altman plots. For this purpose, the score from each

instrument was standardized by subtracting the mean of its scores from the instrument and dividing by the standard deviation of all scores from that instrument. Linear regression methods were used to investigate whether the differences between standardized scores varied systematically with study factors such as sex, age and severity of stroke severity of disability at admission, severity of disability at 3 month follow up and type of stroke.

Results

Characteristics of the total cohort

Characteristics of the 108 participants (66 participants from the cohort study) in the validation study are summarized in **Table 6.1.** The remaining 315 subjects, in the cohort of 381, included 54.9% (173/315) males and with mean age at time of diagnosis of 58.3 (SD 12.8) years for males and 64.7 (SD 14.4) years for females. Ischemic stroke accounted for 76.5% (241/315) of their diagnoses, 41.5% (127/306) had severe impairment at admission, 73.2% (229/315) had severe disability at admission and 43.2% (134/313) had severe disability at three months. In these key respects, the participants in the validation study and non-participants were generally alike. Characteristics of 94 caregivers are summarized in **Table A6.1.**

Table A6.1: Characteristics of caregivers who participated in the study.

Characteristics	%	(n/N)
Age: Mean(SD)	48.3	(12.1)
Female sex	77.0%	(67/87)
Relationship with patients		
Spouse	41.8%	(38/91)
Children	41.8%	(38/91)
Siblings	6.6%	(6/91)
Parents	2.2%	(2/91)
Others	7.6%	(7/91)

Assessment of HRQOL made with EQ-5D

The assessments of HRQoL made with EQ-5D are also shown in Table A6.2. The overall scores were slightly greater (indicating better HRQoL) for males than for females, and decreased with age (r = –0.33), severity of disability at admission (r = –0.45), severity of impairment at admission (r = –0.45) and severity of disability at three months (r = –0.83). Contrary to the results for DHP, they were slightly greater for patients with ICH than for patients with IS. The scores on individual components mirrored the associations with the overall score. With higher scores reflecting poorer HRQoL, the component scores were slightly greater for females but none of the differences by sex reached statistical significance. Consistent with those for EQ-5D, the EQ-5D visual analogue scale (EQ-VAS) scores were slightly greater (indicating better health) for patients with ICH than for patients with IS (p = 0.72). The VAS scores were greater on average (p = 0.40) for men [65.7 (SD 17.9)] than for women [62.3 (SD 23.7)], and decreased with age (r = –0.06), and with severity of impairment at admission (r = –0.19), severity of disability at admission (r = –0.18) and at three months (r = –0.49).

Table A6.2: EQ-5D domains, utility score and visual analogue scale (VAS).

	Male (N=55)		Female (N=53)	
	%	(n/N)	%	(n/N)
Mobility				
No problem	45.5	(25/55)	34.0	(18/53)
Some problem	41.8	(23/55)	56.6	(30/53)
Extreme problem	12.7	(7/55)	9.4	(5/53)
Self-care				
No problem	61.8	(34/55)	54.7	(29/53)
Some problem	9.1	(5/55)	22.6	(12/53)
Extreme problem	29.1	(16/55)	22.6	(12/53)
Usual activity				
No problem	46.3	(25/54)	41.5	(22/53)
Some problem	25.9	(14/54)	26.4	(14/53)
Extreme problem	27.8	(15/54)	32.1	(17/53)
Pain/Discomfort				
No problem	47.3	(26/55)	43.4	(23/53)
Some problem	50.9	(28/55)	49.1	(26/53)
Extreme problem	1.8	(1/55)	7.6	(4/53)
Anxiety/Depression				
No problem	56.4	(31/55)	54.7	(29/53)
Some problem	40.0	(22/55)	37.7	(20/53)
Extreme problem	3.6	(2/55)	7.6	(4/53)
Utility score: Mean (SD*)	0.68	(0.30)	0.67	(0.30)
VAS: Mean (SD*)	65.7	(17.9)	62.3	(23.7

* Standard Deviation

Test and retest reliability of EQ-5D

Additional findings of rank correlation of patient-proxy difference on assessments of DHP dimensions with study factors were shown in **Table A6.3**, **Table A6.4** and **Table A6.5** contains the results for the components of the EQ-5D, its overall score, and the EQ-VAS. Consistent with the re-test measurements made using the DHP, the assessments of HRQoL using the EQ-5D were generally higher on the second occasion. For the EQ-5D utility score, the mean difference of 0.01 (SD 0.04) was significantly greater than zero ($p = 0.02$). The component score with the greatest mean difference was anxiety/depression ($p = 0.11$). After weighting, however, the greatest contributor to the mean difference in EQ-5D overall scores was usual activities ($p = 0.18$), ahead of anxiety/depression ($p = 0.36$). The change in usual activities occurred because six (an unusually large number) of the most severely-affected patients reassessed their capacity to perform usual activities from 3 ("*I am unable to perform my usual activities*") to 2 ("*I have some problems with performing my usual activities*") on the second occasion. On each of the component items, and in respect of the overall score ($p = 0.17$) for which the mean differences were 0.16 (SD 0.50) for men and 0.04 (SD 0.03) for women, the disagreements were principally due to men upgrading their assessment of HRQoL on the second occasion.

Table A6.3: Rank correlation of patient-proxy difference on assessments of DHP dimensions with study factors.

	The DHP dimensions										
	PH	**MH**	**SH**	**Per**	**SE**	**Anx**	**Dep**	**AD**	**Pain**	**Dis**	**GH**
Patient characteristics											
Age	0.17	0.03	0.17	0.15	0.25	0.03	0.11	0.13	-0.02	-0.15	0.22
Female sex	0.15	-0.04	-0.08	-0.03	0.02	0.10	0.06	-0.12	-0.12	0.00	0.07
Severe stroke at admission	-0.11	0.00	-0.03	-0.03	-0.03	-0.16	-0.10	-0.14	-0.19	-0.12	-0.13
Severe disability at admission	-0.13	-0.13	-0.03	0.15	-0.02	-0.15	-0.23	-0.18	-0.15	-0.15	-0.13
Severe disability at three months	-0.03	-0.14	0.13	0.20	0.02	-0.09	-0.18	-0.16	-0.17	-0.08	-0.05
Proxy characteristics											
Age	0.15	-0.03	0.05	-0.05	-0.02	-0.02	0.03	-0.04	0.06	-0.04	0.05
Female sex	0.01	-0.01	0.01	0.06	-0.19	-0.11	-0.16	-0.20	-0.03	0.09	-0.13

PH: physical health, MH: mental health, SH: social health, Per: perceived health, SE: self-esteem, Anx: anxiety, Dep: depression, AD: anxiety-depression, Dis: disability, GH: general health.

Table A6.4: Test and retest reliability of measurements of HRQoL made one week apart of patient responses to the EQ-5D.

	Test		Re-test		Difference				
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**ICC***	**SEM†**	**MDD‡**
Morbidity	0.094	(0.123)	0.092	(0.129)	-0.001	(0.052)	0.915	0.037	0.102
Self-care	0.043	(0.058)	0.041	(0.056)	-0.001	(0.024)	0.909	0.017	0.048
Usual activity	0.076	(0.089)	0.068	(0.084)	-0.007	(0.052)	0.818	0.037	0.103
Pain/Discomfort	0.025	(0.033)	0.025	(0.033)	0	(0.023)	0.777	0.017	0.046
Anxiety/Depression	0.026	(0.038)	0.027	(0.037)	0.004	(0.042)	0.433	0.030	0.083
EQ-5D overall score	0.676	(0.299)	0.686	(0.304)	0.010	(0.04)	0.989	0.031	0.084
VAS	64.1	20.9	64.7	(18.4)	1.00	(18.8)	0.545	13.20	30.80

* ICC= Intra-class Correlation Coefficient,
† SEM= Standard Error of Measurement,
‡ MDD= Minimal Detectable Difference

Table A6.5: Percent agreement and weighted Kappa for test-retest measurements made one week apart of patient responses to the EQ-5D.

EQ-5D components	Percent agreement	Weighted Kappa
Morbidity	96.3%	0.86
Self-esteem	94.1%	0.86
Usual activity	91.6%	0.80
Pain/discomfort	93.8%	0.65
Anxiety/Depression	87.3%	0.40

The test-retest differences were not influenced strongly by age (r = 0.03), type of stroke (r = 0.20), severity of impairment (r = 0.06), or severity of disability at admission (r = 0.11) and at three months (r = -0.04). Inspection of Bland-Altman plots of difference against average did not reveal systematic patterns in the differences or greater than expected numbers of outlying values. The greatest number of differences (n=35) occurred on re-measurement of anxiety. The intra-class correlation coefficients (ICC) ranged from 0.41 for anxiety to 0.89 for self-care. It was 0.99 for the overall score, in which the component scores are weighted and the penalty for the overwhelmingly most frequent change (moving from 1 = least severely affected to 2 = moderately affected, or conversely) is minor.

Consistent with the measurements made by the DHP and EQ-5D, the EQ-VAS scores on the EQ-5D instrument were generally greater on re-test but the mean difference was small (p = 0.58). The mean differences were almost identical for males (1.02 [SD 16.6]) and females (1.00 [SD 20.8]) and, whilst not influenced strongly by the following factors, decreased with age (r = –0.08), severity of impairment at admission (r= –0.12), severity of disability at admission (r = –0.08) and at three months (r = –0.02). Inspection of Bland-Altman plots of difference against average did not reveal systematic patterns in the differences or greater than expected numbers of outlying values. Reflecting the greater contribution of within-person differences, the ICC was moderate (0.56).

Patient-proxy reliability of EQ-5D

Also shown in **Table A6.6** and **Table A6.7** are the mean proxy-patient differences for components of the EQ-5D and its overall score, and for the EQ-VAS. The assessments of morbidity (p = 0.16), usual activity (p = 0.06) and pain (p = 0.37) using the EQ-5D were greater on proxy assessment. For all components of EQ-5D, the proxy-patient differences were more extreme when the proxy was a male than when the proxy was a female but these differences were not statistically significant. The proxy-patient differences in self-care (p = 0.01), usual activity (p = 0.01) and EQ-5D overall score (p = 0.01) were associated with age of the patient. For most EQ-5D components, the proxy-patient differences were greater for patients with ischemic stroke and for patients with severe impairment or disability at admission or severe disability after three months.

Table A6.6: Patient-proxy reliability of measurements of HRQoL using the EQ-5D.

	Test		Re-test		Difference				
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**ICC***	**SEM†**	**MDD‡**
Morbidity	0.100	(0.130)	0.094	(0.132)	-0.006	(0.068)	0.845	0.049	0.134
Self-care	0.459	(0.596)	0.047	(0.059)	0.014	(0.031)	0.854	0.022	0.060
Usual activity	0.084	(0.091)	0.074	(0.088)	-0.089	(0.046)	0.855	0.033	0.091
Pain/Discomfort	0.027	(0.035)	0.026	(0.037)	-0.001	(0.034)	0.513	0.024	0.067
Anxiety/Depression	0.026	(0.038)	0.029	(0.047)	0.003	(0.039)	0.571	0.027	0.076
EQ-5D overall score	0.66	(0.31)	0.67	(0.32)	0.01	(0.16)	0.858	0.113	0.160
VAS	63.0	(20.5)	62.7	(18.8)	-1.40	(18.8)	0.539	13.25	36.74

* ICC= Intra-class Correlation Coefficient,
† SEM= Standard Error of Measurement,
‡ MDD= Minimal Detectable Difference

Table A6.7: Percent agreement and weighted Kappa for measurements of patient responses and proxy responses to the EQ-5D.

EQ-5D components	Percent agreement	Weighted Kappa
Morbidity	95.4%	0.84
Self-esteem	93.3%	0.85
Usual activity	93.0%	0.84
Pain/discomfort	91.0%	0.56
Anxiety/Depression	88.6%	0.51

The proxy-patient differences on EQ-5D were relatively smaller than those on the DHP, and without a consistent pattern but with proxies providing slightly lower HRQoL assessments overall and on the EQ-VAS. The stratified results indicate that, other than by the EQ-VAS, male proxies tend to over-estimate HRQoL relative to patients and/or relative to female proxies (data not shown), and that female proxies tend to underestimate HRQoL relative to patients and/or relative to male proxies (data not shown). The ICC for proxy-patient variation in overall EQ-5D was lower, and the ICC for the anxiety component was higher, but otherwise the ICCs were generally similar to the corresponding values for patient test-retest.

Chapter 7: Health-related quality of life among survivors three month after stroke

7.1. Preface

In previous chapters, the case-fatality and functional outcomes following stroke of survivors in a cohort of patients with first-ever stroke. An assessment of their health-related quality of life (HRQoL), measured using the tool assessed the reliability and validity in Chapter 6, is presented in this chapter to provide more evidence of the current burden of stroke in Viet Nam. At the time of thesis submission, the texts of this chapter and had been prepared as a manuscript for submission in consideration of publication in the Stroke journal. The appendix to this chapter (Appendix 7) has been prepared as online supplementary data for the manuscript.

7.2. Introduction

In recent years, mortality rates from stroke have been decreasing in both HICs and LMICs due to better treatment [2]. As a result of the neurologic impairments caused, however, approximately 30%-40% of all patients with stroke require assistance three months after the stroke to perform basic activities of daily living [159]. Although case-fatality and functional status following stroke have been assessed in a few studies conducted in LMICs, there is limited understanding of how stroke influences patients' lives. Quantifying the impacts that the symptoms, impairments and psychological sequela associated with stroke have on the individual's QoL enables a more comprehensive understanding of the extent of the burden caused by the disease and its treatment, and this has been emerging as a particular need in LMICs.

QoL can be defined in both a general sense and in a health-related context. HRQOL has been defined by the WHO as "an integrative measure of physical and emotional well-being, level of independence, social relationships and their relationship to salient features of their environment" [192]. HRQoL is thus both subjective and multidimensional.

The limited investigations conducted to date in LMICs have shown that, relative to apparently healthy adults or population norms, survivors of stroke have reduced HRQoL particularly in domains related to physical functioning [238,241,242]. The first three months after stroke have been found to be a critical time for improvement in physical functioning and HRQoL in Taiwan and Thailand [241,236]. In studies conducted in both HICs and LMICs, poorer HRQoL among survivors of stroke has been associated with advanced age, female sex, lower socio-economic status, more severe stroke and poorer functional status [241,245].

Given the subjectivity of HRQoL assessment and differences in cultural values that influence specific dimensions [250], it is not certain that these findings are generalizable to other countries such as Viet Nam where patients with stroke on average are of younger age, have more severe symptoms at stroke onset and more functional disability at three month post-stroke [334] (Chapter 3) compared to those from HICs. To date there are limited data on HRQoL of survivors of stroke in Viet Nam. The aims of this study were to assess the HRQoL of first-ever stroke survivors at three month post stroke in Viet Nam, and to identify factors related to poor HRQoL.

7.3. Methods

Participants

The participants were a consecutive series of stroke patients from the stroke unit at 115 People's Hospital, which is a major teaching hospital in Ho Chi Minh City, Viet Nam. Patients were eligible if they had suffered a first-ever ischaemic or haemorrhage stroke confirmed by a neurologist, were aged>16 years, lived in Ho Chi Minh City, the stroke had occurred within the preceding 7 days, and treatment was received within the stroke unit. We excluded patients with recurrent stroke and early discharge to home (usually with a poor prognosis). Recruitment commenced on the 1st of June 2012 and continued until the targeted number of 450 eligible subjects (from 960 admissions) was reached on the 10th of September 2012.

Data collection

During the hospital admission, stroke and type of stroke were confirmed by a neurologist in the Stroke Unit using the standard clinical definition of sudden onset of focal neurological symptoms of presumed vascular origin, with all patients receiving brain imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] to exclude other causes of neurological symptoms and to define stroke type. Severity of neurological impairment graded on the NIHSS [115], and functional status graded on the mRS [122], were assessed by a neurologist on the Stroke Unit.

Patients or their main caregivers were interviewed by research assistants to collect data on (1) socio-demographic factors such as marital status, education, job and working status; (2) health insurance; (3) economic status such as household assets, monthly income and monthly expenditure per household; (4) lifestyle risk factors, such as tobacco smoking and alcohol consumption; and (5) health status before stroke, including disability and co-morbidities such as hypertension, diabetes, heart disease, chronic lung disease, chronic liver disease, chronic renal disease and cancer.

Three months after stroke, patients were interviewed in their homes to assess their HRQoL and functional status. Functional status was again graded on the mRS. When the patient had severely impaired cognition, the main caregiver provided information on behalf of the patient. The Duke Health Profile (DHP) and EQ-5D health questionnaires were used to assess the HRQoL of patients.

The DHP is a generic, self-report HRQoL instrument with a reference period either of today or the past week. Full details of the instrument are given in the online supplement. In brief, the six domains of health function comprise physical health, mental health, social health, general health, perceived health and self-esteem, and greater scores indicate better health. The four domains of health dysfunction comprise anxiety, depression, pain and disability, and higher scores indicate poorer health. The scoring was reversed for the four dysfunctional domains so that the scores on each domain range from 0 (poorest health) to 100 (best possible health). The general health domain provides a summary score covering physical health, mental health and social health.

The EQ-5D refers to current health. It comprises 5 components: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the respondent's self-rated health on a visual analogue scale (VAS) with the endpoints labelled as "*Best imaginable health state*" and "*Worst imaginable health state*". To calculate an overall EQ-5D utility score [range -0.263 (worst) to 1 (best)], the components were summed using weights

for the South Korean general population [296] in the absence of a value set for Viet Nam. The mean EQ-5D utility score of stroke patients aged more than 60 years was compared to that of a study sample of 2873 persons over 60 years of age from the rural community of FilaBavi in the north of Viet Nam [231]. The latter study also used the South Korean value set to calculate the EQ-5D utility score.

Data analysis

Summary values are presented as median and interquartile range (IQR) and/or as mean and standard deviation (SD) for continuous data, and as percentages for categorical data. For each DHP dimension, mean scores were calculated over non-missing item scores if less than 50% of item scores were missing. Mean scores were calculated for the entire sample and with stratification by sex, age, severity of impairment, severity of functional status and type of stroke. Linear regression methods were used to estimate mean differences in DHP dimension scores and the EQ-5D utility and VAS scores according to differing patient characteristics such as age, sex, and stroke severity. Functional status graded on the mRS was grouped into 3 levels of impaired functional outcome (disability): least severe (mRS=0/1), moderate (mRS=2/3) and most severe (mRS=4/5). All statistical tests were two-sided with a 5% allowance for type I error. To compare mean DHP scores and EQ-5D utility scores of stroke patient with population values, the age- and sex- specific mean scores of a general adult population of Ho Chi Minh City [213] were weighted to the age-and sex-distribution of the stroke patients, and the age-specific mean scores of the FilaBavi sample [231] were weighted to the age-distribution of the stroke patients.

7.4. Results

During the recruitment process, there were 441 patients completing the baseline interview. Of these, 38 were confirmed to have died during follow-up over the next three months, 27 were lost to follow-up and 4 refused assessment of HRQoL at the planned interview three months post-stroke. The remaining 372 participants were followed up to three month and are included in this study (**Table 7.1**).

Table 7.1: Baseline characteristics and three-month functional status in three-month survivors of first-ever stroke in Ho Chi Minh City, Viet Nam.

	Men (n=204)	Women (n=172)
Age		
Mean (SD)	58.6 (12.3)	64.3 (14.2)
Median (IQR)	57.0 (49-68)	64.0 (53-76)
< 45 years	12.4% (25)	7.0% (12)
45-54 years	28.9% (58)	19.9% (34)
55-64 years	26.9% (54)	23.4% (40)
65-74 years	20.9% (42)	18.7% (32)
75+ years	11.0% (22)	31.0% (53)
Marital status *		
Married	92.0% (185)	59.1% (101)
Single	4.0% (8)	5.3% (9)
Divorced	1.5% (3)	1.8% (3)
Widowhood (widower/widow)	2.5% (5)	33.9% (58)

	Men (n=204)	Women (n=172)
Highest education level *		
No schooling	15.9% (32)	46.2% (79)
Grades 1–5	22.9% (46)	29.8% (51)
Grades 6–9	23.9% (48)	15.2% (26)
Grades 10–12	23.9% (48)	7.0% (12)
College/university	13.4% (27)	1.8% (3)
Working status *		
Manual work	28.6% (57)	6.4% (11)
Office work	20.1% (40)	17.0% (29)
Home duties/retired	51.3% (102)	76.6% (131)
Living with spouse *		
Yes	79.0% (158)	39.6% (67)
No – living with children	16.0% (32)	53.9% (91)
No – living with others	5.0 (10)	6.5% (11)
Comorbidity *		
No	77.6% (156)	65.5% (112)
1	16.4% (33)	25.7% (44)
2+	6.0% (12)	8.8% (15)
Pre-stroke disability *		
No	96.0% (193)	91.2% (156)
Yes	4.0% (8)	8.8% (15)
Type of stroke		
Ischaemic stroke	72.1% (145)	80.7% (138)
ICH	27.9% (56)	19.3% (33)
Severity of impairment (NIHSS) †		
Mean score (SD)	7.3 (5.3)	8.0 (5.6)
Severe (NIHSS> 7)	38.5% (75)	43.0% (71)
Not severe (NIHSS≤ 7)	61.5% (120)	57.0% (94)
Functional status (mRS) †		
Mean score (SD)	3.1 (1.1)	3.1 (1.1)
Least severe (mRS=0/1)	12.1% (24)	12.9% (22)
Intermediate (mRS=2/3)	44.7% (89)	40.0% (68)
Most severe (mRS=4/5)	43.2% (86)	47.1% (80)
Functional status (mRS) at follow-up ‡		
Mean score (SD)	2.1 (1.4)	2.7 (1.4)
Least severe (mRS=0/1)	41.3% (83)	25.2% (43)
Intermediate (mRS=2/3)	35.3% (71)	41.5% (71)
Most severe (mRS=4/5)	23.4% (47)	33.3% (57)

* Patient self-report.
† Assessed during initial hospital stay
‡ Assessed at follow-up three months post-stroke

They comprised 54.3% (204/376) men with a mean age of 61.2 (SD 13.4) years. Women were approximately 6 years older than men, and only one quarter of them were still working at stroke onset compared to half of the men. Almost all of the men, but only three-fifths of the women, were married with one-third of the women having been widowed and with three-fifths of them living with children or others. Men had greater educational attainment than women.

The majority of patients had suffered an ischaemic stroke (IS). Women more often had co-morbidities and a greater average severity of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS) at admission than men. At follow-up more women had impaired functional status at three month than men. Men and women had similar mean scores for the DHP dimensions of social health, self-esteem and disability but on other dimensions the mean scores of men were markedly more than for women (**Table 7.2**).

For general health, which provides an overall score for DHP dimensions other than perceived health and disability, the mean score in men was 7.7 points (14%) more than that of women and this difference was high relative to sampling variability. Men also performed better on the EQ-5D utility scores and VAS scores. On the EQ-5D utility score, 6.7% (25/373) of survivors had assessments of HRQoL that were negative (rated as worse than death).

Adjustments were made for proxy assessments (n=48) as these were on average 27.2% lower than assessments for patients who provided their own information. The mean values of the DHP decreased with age group, were greater for men than for women, and were greater for those with greater severity of neurological impairment and impaired functional status at admission (**Table 7. 2**).

Table 7.2: Mean scores of DHP dimensions, EQ-5D utility, and visual analogue scale (VAS) in three-month survivors of stroke.

	All	Male (n=201)	Female (n=172)
	Mean (SD)	Mean (SD)	Mean (SD)
DHP			
Physical health	53.5 (26.7)	60.1 (26.4)	45.7 (25.0)
Mental health	64.4 (24.8)	67.5 (23.9)	60.8 (25.5)
Social health	57.7 (15.2)	58.5 (15.8)	56.8 (14.4)
General health	58.7 (17.8)	62.2 (17.4)	54.5 (17.5)
Perceived health	28.7 (36.1)	32.0 (36.8)	24.9 (35.0)
Self-esteem	75.1 (18.8)	76.3 (17.9)	73.7 (19.8)
Anxiety	72.5 (20.1)	74.5 (19.4)	70.2 (20.7)
Depression	66.4 (24.3)	70.6 (22.9)	61.6 (25.1)
Pain	63.7 (35.8)	70.0 (34.0)	56.4 (36.6)
Disability	69.0 (43.1)	69.5 (43.1)	68.3 (43.2)
EQ-5D			
Utility score	0.67 (0.33)	0.72 (0.31)	0.62 (0.34)
VAS	61.3 (20.4)	64.1 (20.1)	58.0 (20.4)

There were also sex differences in the dimensions of physical health, mental health, self-esteem, depression and pain (**Tables A7.1**-**Table A7.3** in Appendix 7). The mean DHP general health score of those with least severity of impaired functional status (mRS=0/1) at admission was similar to that of a general population sample of Ho Chi Minh City (**Table A7.4**-**Table A7.10** in Appendix 7).

Age-adjusted to the sex-specific distribution of the patients with stroke, the mean overall score of the population sample was 62.8 (SD 18.2). In patients with intermediate severity of stroke at admission (mRS=2/3) the mean DHP general health score was 5.1 points less than the general population and 14.3 less points than those with the most severe severity of impaired functional status (mRS=4/5).

Three months later those with the least severity of impaired functional status (mRS=0/1) had a substantially greater mean DHP general health score than the general population sample. Those in each grouping of functional status at three month had similar mean DHP general health scores irrespective of the severity of their impaired functional status at admission (**Table 7.3**). Similar results were found for the EQ-5D utility scores and EQ-5D VAS scores.

The mean EQ-5D utility score of stroke survivors who were aged greater than 60 years, age adjusted to a rural community in the north of Viet Nam, was 0.58 (SD 0.35) (**Table A7.11** in Appendix 7), compared to 0.88 for those living in the rural population. Similar to the DHP general health score, survivors of stroke with least severity of impaired functional status (mRS=0/1) at three months had a greater EQ-5D utility score (0.95) than the rural population sample (0.88). Patients with intermediate impaired functional status (mRS=2/3) or most severe impaired functional status (mRS= 4/5) at three months had lower EQ-5D utility score than that of the rural population.

The mean DHP general health score, EQ-5D utility score and EQ-5D VAS score between levels of the study factors were attenuated when adjusted for age, sex severity of impairment, and proxy response (**Table 7.4**). Further adjustment for impaired functional status at three months further attenuated the differences.

For each of the HRQoL dimensions, the differences in mean scores between subjects classified by level of impaired functional status at three months were statistically significant, and only the sex differences for the DHP dimensions of physical health, depression, pain and impaired functional status remained statistically significant after adjustment for the grouped mRS levels of impaired functional status at three months (**Tables A7.12**-**Table A7.14** in Appendix 7).

Table 7.3: Mean scores* of DHP general health, EQ-5D utility and visual analogue scale (VAS) in three-month survivors of stroke.

	DHP general health (n=369)		EQ-5D utility score (n=372)		EQ-5D VAS (n=367)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Age						
<45 years	37	67.6 (62.5, 77.8)	37	0.83 (0.72, 0.93)	37	72.1 (66.0, 78.2)
45-54 years	92	60.0 (56.6, 63.3)	92	0.75 (0.69, 0.82)	91	62.4 (58.4, 66.4)
55-64 years	94	62.2 (58.9, 65.5)	94	0.71 (0.64, 0.77)	92	64.9 (60.9, 68.8)
65-74 years	73	54.5 (50.7, 58.3)	74	0.54 (0.47, 0.61)	74	57.8 (53.4, 62.3)
75+ years	73	54.6 (50.7, 58.5)	75	0.51 (0.44, 0.58)	73	56.3 (51.8, 60.9)
Trend		**-2.9 (-4.2, -1.5)†**		**-0.09 (-0.11, -0.1)***		**-3.2 (-4.8, -1.6)***
Sex						
Male	199	62.5 (60.3, 64.8)	201	0.70 (0.66, 0.75)	200	64.4 (61.7, 67.1)
Female	170	55.2 (52.7, 57.7)	171	0.60 (0.55, 0.65)	167	58.8 (55.8, 61.8)
Difference		**-7.4 (-10.7, -4.0)***		**-0.11 (-0.17, -0.04)***		**-5.6 (-9.7, -1.6)***
Marital status						
Married	89	60.8 (58.9, 62.7)	286	0.68 (0.65, 0.72)	284	63.7 (61.4, 66.0)
Single	79	63.5 (55.8, 71.2)	17	0.73 (0.57, 0.89)	17	58.9 (49.5, 68.2)
Divorced	96	49.1 (35.6, 62.6)	6	0.69 (0.42, 0.96)	6	66.4 (51.0, 81.9)
Widowhood(widower/widow)	99	50.8 (46.5, 55.0)	63	0.50 (0.42, 0.58)	60	55.5 (48.5, 58.6)
Wealth index						
1st quarter (richest)	89	63.1 (59.7, 66.5)	91	0.65 (0.58, 0.72)	87	63.8 (59.7, 68.0)
2nd quarter	79	57.7 (54.0, 61.4)	80	0.62 (0.55, 0.70)	80	60.5 (56.1, 64.8)
3rd quarter	96	57.6 (54.2, 61.0)	96	0.63 (0.56, 0.70)	96	60.3 (56.3, 64.3)
4th quarter (poorest)	99	58.4 (55.1, 61.7)	99	0.71 (0.64, 0.78)	98	62.7 (58.8, 66.6)
Trend		-1.4 (-3.0, 0.1)		0.02 (-0.01, 0.05)		-0.3 (-2.2, 1.5)
Type of stroke						
ICH	89	56.9 (53.4, 60.4)	89	0.58 (0.51, 0.65)	88	59.6 (55.5, 63.8)
IS	280	59.9 (59.9, 57.9)	283	0.68 (0.64, 0.72)	279	62.6 (60.3, 64.9)
Difference		2.9 (-1.1, 7.0)		0.10 (0.02, 0.18)		3.0 (-1.8, 7.7)

	DHP general health (n=369)		EQ-5D utility score (n=372)		EQ-5D VAS (n=367)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Severity of impairment						
NIHSS≤ 7	212	63.1 (60.9, 65.2)	214	0.77 (0.73, 0.82)	210	65.8 (63.3, 68.4)
NIHSS> 7	145	53.7 (51.1, 56.4)	146	0.49 (0.45, 0.54)	145	56.3 (53.1, 59.5)
Difference		**-9.3 (-12.8, -5.9)***		**-0.28 (-0.34, -0.22)***		**-9.5 (-13.6, -5.4)***
Disability at 3 month						
Least severe (mRS= 0/1)	126	71.8 (69.5, 74.1)	126	0.93 (0.90, 0.96)	124	75.1 (72.2, 78.0)
Least severe at admission	27	73.2 (68.4, 78.1)	27	0.93 (0.87, 0.99)	26	71.9 (65.6, 78.2)
Intermediate at admission	70	71.7 (68.6, 74.7)	70	0.93 (0.89, 0.97)	69	77.1 (73.2, 81.0)
Most severe at admission	29	71.0 (66.3, 75.8)	29	0.92 (0.86, 0.98)	29	73.3 (67.3, 79.2)
Intermediate (mRS=2/3)	140	57.6 (55.4, 59.8)	140	0.74 (0.72, 0.77)	141	60.3 (57.5, 63.1)
Least severe at admission	19	57.2 (53.7, 60.8)	19	0.74 (0.67, 0.82)	19	58.1 (50.5, 65.8)
Intermediate at admission	55	57.2 (53.7, 60.8)	56	0.78 (0.73, 0.82)	55	60.7 (56.2, 65.2)
Most severe at admission	64	58.6 (55.3, 61.9)	65	0.71 (0.67, 0.75)	65	49.0 (42.9, 55.2)
Most severe (mRS=4/5)	102	45.6 (42.9, 48.4)	104	0.28 (0.25, 0.32)	102	47.5 (44.1, 51.0)
Least severe at admission	0	n.a.	0	n.a.	0	n.a.
Intermediate at admission	30	47.0 (52.0, 52.1)	31	0.38 (0.32, 0.44)	31	49.0 (42.9, 55.2)
Most severe at admission	72	45.0 (41.6, 48.3)	72	0.24 (0.20, 0.28)	70	47.2 (43.0, 51.4)
Trend †		**-13.4 (-15.3, -11.5)**		**-0.32 (-0.34, -0.30)**		**-14.1 (-16.5, -11.7)**

* denotes p<0.05

†Trend over three category means

Table 7.4: Mean scores* and difference in mean scores of the DHP general health, EQ-5D utility and visual analogue scale (VAS) in three-month survivors of stroke.

	DHP general health		EQ-5D utility score		EQ-5D VAS	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Age						
< 45 years	68.8(63.9, 73.7)	62.9(58.7, 67.2) †	0.85(0.75, 0.94)	0.71(0.66, 0.77)	72.3(66.3, 78.3)	65.5(60.1, 70.9)
45-54 years	**-9.5(-15.3, -3.7)**	**-5.4(-10.3, -0.5)**	-0.11(-0.22, 0)	0 (-0.06, 0.06)	-10.2 (-17.4, -3.1)	-5.4 (-11.7, 0.9)
55-64 years	**-7.1(-12.9, -1.3)**	-2.1(-7.0, 2.8)	**-0.16(-0.27, -0.05)**	-0.03 (-0.09, 0.03)	-8.2 (-15.3, -1.1)	-2.7 (-9.0, 3.6)
65-74 years	**-14.6(-20.7, -8.5)**	-5.2(-10.5, 0.09)	**-0.29(-0.40, -0.17)**	-0.06 (-0.13, 0.01)	-14.6 (-22.1, -7.2)	-3.9 (-10.7, 2.8)
75+ years	**-12.5(-18.8, -6.3)**	-3.0(-8.4, 2.4)	**-0.30(-0.42, -0.19)**	-0.06 (-0.13, 0.01)	**-14.4 (-22.1, -6.8)**	-3.7 (-10.6, 3.2)
Trend	**-2.6(-3.9, -1.3)**	-0.2(-1.3, 1.0)	**-0.08(-0.1, -0.05)**	**-0.02 (-0.03, 0)**	**-2.9 (-4.5, -1.3)**	-0.2 (-1.7, 1.2)
Sex						
Male	61.7(59.6, 63.9)	61.0 (59.2, 62.8) †	0.68(0.64, 0.72)	0.68 (0.65, 0.70)	63.2 (60.6, 65.9)	62.3 (60.0, 64.6)
Female	**-5.3(-8.6, -2.0)**	**-3.3(-6.0, -0.5)**	-0.03(-0.09, 0.03)	0.01 (-0.02, 0.05)	-2.9 (-6.9, 1.1)	-0.8 (-4.2, 2.7)
Marital status						
Married	59.8(58.0, 61.7)	59.8(58.3, 61.3) †	0.66(0.63, 0.70)	0.68 (0.66, 0.70)†	62.8 (60.5, 65.0)	62.7 (60.7, 64.6)
Single	5.1(-2.8, 13.0)	5.5(-1.0, 11.9)	0.02(-0.12, 0.16)	0.04 (-0.04 0.12)	-7.3 (-17.1, 2.6)	-6.9 (-15.4, 1.6)
Divorced	-12.0(-24.7, 0.8)	-10.8(-21.3, -0.2)	-0.02(-0.24, 0.20)	0 (-0.13, 0.13)	2.0 (-13.0, 17.1)	3.4 (-9.5, 16.2)
Widowhood	-3.3(-8.4, 1.8)	-2.6(-6.8, 1.6)	-0.03(-0.12, 0.06)	-0.02 (-0.07, 0.04)	-3.8 (-10.1, 2.5)	-2.9 (-8.3, 2.5)
Wealth index †						
1st quarter (richest)	64.5(61.3, 67.7)	61.9 (59.1, 64.6)†	0.69 (0.63, 0.75)	0.65(0.62, 0.69)	65.1(61.1, 69.0)†	62.0(58.5, 65.5)
2nd quarter	**-7.1(-11.8, -2.4)**	-2.8 (-6.8, 1.2)	-0.07(-0.15, 0.02)	0.02(-0.03, 0.07)	-4.9(-10.7, 0.9)	-0.4(-5.5, 4.7)
3rd quarter	**-7.5(-11.9, -3.0)**	-3.8 (-7.5, 0)	-0.05(-0.14, 0.03)	0.03(-0.02, 0.08)	-4.9(-10.4, 0.6)	-0.8(-5.6, 4.0)
4th quarter (poorest)	**-5.9(-10.4, -1.5)**	-2.8 (-6.6, 1.0)	0(-0.08, 0.08)	0.07(0.02, 0.11)	-3.1(-8.6, 2.5)	0.7(-4.2, 5.6)
Trend	**-1.8(-3.3, -0.4)**	-0.9 (-2.1, 0.3)	0(-0.02, 0.03)	**0.02(0, 0.04)**	-0.9(-2.7, 0.9)	0.2(-1.4, 1.7)

	DHP general health		EQ-5D utility score		EQ-5D VAS	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Type of stroke						
ICH	58.2(54.6, 61.8)	58.9(55.9, 61.9) †	0.61(0.55, 0.68)†	0.66(0.62, 0.69)	60.6(56.2, 65.0)	61.1(57.3, 64.9)
IS	1.4(-2.7, 5.6)	0.7(-2.7, 4.1)	0.06(-0.01, 0.13)	0.03(-0.01, 0.07)	1.7(-3.4, 6.7)	1.1(-3.2, 5.5)
Severity of impairment						
NIHSS ≤ 7	62.8(60.7, 64.9)	59.3(57.5, 61.1) †	0.77 (0.73, 0.81)	0.70(0.68, 0.72)	65.6(63.1, 68.1)	61.6 (59.3, 63.9)
NIHSS > 7	**-8.7(-12.0, -5.3)**	0.4(-2.6, 3.4)	**-0.27(-0.33, -0.21)**	-0.05(-0.09, 0)	**-8.9(-13.0, -4.9)**	0.9(-2.9, 4.8)
Disability						
Least severe (mRS=0/1)	62.6(57.8, 67.4)	59.3(55.2, 63.3) †	0.72(0.63, 0.81)	0.66(0.61, 0.71)	61.2(55.2, 67.1)	57.6(52.5, 66.3)
Intermediate (mRS=2/3)	**-2.9(-8.0, 2.3)**	0.2(-4.1, 4.5)	-0.03(-0.13, 0.06)	0.04(-0.02, 0.09)	2.5(-3.9, 8.9)	5.9(0.4, 11.5)
More severe (mRS=4/5)	**-4.3(-10.2, 1.6)**	0.5(-4.5, 5.5)	-0.10(-0.20, 0.01)	0.01(-0.05, 0.08)	-0.7(-8.1, 6.6)	4.0(-2.4, 10.4)
Trend	-2.0(-4.9, 0.9)	-0.4(-5.7, 4.9)	-0.05(-0.10, 0)	0(-0.03, 0.03)	-0.9(-4.5, 2.6)	1.2(-1.9, 4.3)
Disability at 3 months						
Least severe (mRS=0/1)	71.0(68.5, 73.5)	n.n.	0.90(0.87, 0.93)	n.n.	74.0(70.8, 77.3)	n.n.
Intermediate (mRS=2/3)	**-12.8(-16.1, -9.5)**		**-0.15(-0.19, -0.11)**		**-13.5(-17.8, -9.2)**	
More severe (mRS=4/5)	**-24.9(-29.3, -20.5)**		**-0.57(-0.63, -0.52)**		**-25.6(-31.2, -20.0)**	
Trend	**-12.7(-15.0, -10.5)**		**-0.28(-0.31, -0.25)**		**-13.0(-15.9, -10.2)**	

* Adjusted for age, sex, proxy response and severity of impairment at admission

7.5. Discussion

In this follow-up at three months of a cohort of first-ever stroke patients in Ho Chi Minh City, Viet Nam, the stroke patients on average had lower HRQoL than both the general population of Ho Chi Minh City [213], and a rural community in the north of Viet Nam [231]. Women had poorer HRQoL than men. The poor HRQoL was most evident in those with the greatest impaired functional status at three months. Surprisingly, those with the least severity of impaired functional status at three months had greater HRQoL than the general population sample from Ho Chi Minh City [213] and rural Viet Nam [231].

The mean EQ-5D utility score (0.67) at three months of the Vietnamese stroke patients in this study was similar to that reported for people with stroke in Sweden (mean utility score 0.65, mean age 63.2 years) [350], Canada (mean utility score 0.70, mean age 67.3 years) [351] and Singapore (mean utility score 0.65) [238]. In this study, 6.7% of stroke survivors rated their HRQoL was poorer than death (negative utility score) compared to 12.5% of generally older (by almost a decade) stroke survivors in a multi-centre trial of the efficacy of nitric oxide (ENOS) [352]. When comparing the QoL among the general population, previous investigators [227,241,353] found that survivors of stroke at three months on average had poorer HRQoL assessed using the SF-36 than the persons accompanying them to hospital. Studies using EQ-5D and other instruments [236-238] have found the HRQoL of long-term stroke patients to be lower than the norm for their population. Hackett et al. [240] and Shyu et al. [236] found that physical and social functioning were significantly lower among stroke survivors than was normal for their populations [213,231,238,350-352].

Notably, the long-term stroke survivors with compromised physical and social functioning in an Auckland study using the SF-36 nevertheless had mental health comparable to the norm [240]. In this study, there were much larger differences at three months on some DHP dimensions than others, and the reduced mental health relative to population values was marked only among those with most severe disability (mRS=4/5). This was true also for DHP physical health, and for DHP general health that combines scores for the DHP physical, mental and social health dimension. For patients overall, the EQ-5D seemed most sensitive in detecting divergence from population values. If this is not an artefact of different population samples, it may be because the DHP is a generic questionnaire that covers multiple dimensions of HRQoL. In this study, some of these – social health, self-esteem, anxiety and depression – appeared unresponsive to stroke in the sense that even for the most severely impaired functional patients, there were only minor divergences from the mean values for the population sample. The EQ-5D is not a stroke-specific questionnaire either, but it places relatively more focus on physical health and functioning that were markedly poorer for the most severely disabled patients in this study [1].

In developed countries, survivors of stroke are commonly found to have poorer mental and social HRQoL than the general population [241,245]. That was not the case in our study. While this could be due to inadequacies of the DHP instrument in detecting the psychological and social aspects of coping with stroke, it is also possible that cultural differences could play a role. After having a stroke in developed countries, many stroke survivors are moved from their home to a nursing home or rehabilitation centre due to the absence of an available caregiver [354,355]. In contrast, in Viet Nam, survivors of stroke mostly stay in their usual home with support and care from close family members. While the burden of caring for a stroke patient can cause problems for the caregiver, such care has been shown to improve the mental health and social health of stroke survivors. For example, Theeke et al. [356] showed

that patients who were discharged to a nursing home had poorer QoL at three months than those who were discharged to home after controlling for age, sex and comorbidity. In a Nigerian study [357], the functional and mental status of stroke survivors improved with the involvement of the stroke patient's spouse as the caregiver [357]. This finding is consistent with those of others where active partnership with important family members or main caregivers influences the success of self-management of patients with chronic illness [358,359].

The factors that we found to be associated with HRQoL across domains and instruments at three months were broadly consistent with those reported from studies conducted in developed countries. These included older age [227,353], female sex [302,360,361], stroke severity [227,241,353] and poor functional status after stroke [227,241,249,353,362]. Of these, only female sex was a predictor of HRQoL at three months in this study independently of attained functional status. The findings in relation to functional status are consistent with previous findings in respect of short-term [360] and long-term [245,363,364] outcomes of stroke. Some authors have suggested that poorer HRQoL among female stroke patients [227,245,365-367] is mainly due to advancing age, lower socioeconomic status, higher prevalence of impaired functional status, comorbidities and depressive symptoms. In this study, the women with stroke reported poorer HRQoL than men after adjustment for age, proxy response, severe of stroke at admission and functional status at three months. In general, women report poorer HRQoL than men in general population studies [368-370] including those conducted in Viet Nam [213,231], and in studies of patient groups including those with general chronic disease [371], chronic obstructive pulmonary disease [372], sarcoidosis [373], diabetes [374] and lumbar spinal stenosis [375]. In relation to stroke, studies in HICs have identified sex differences in access to and effectiveness of stroke treatment and rehabilitation therapy [25,175,376]. Relatively fewer of the female patients than of the male patients in this cohort had improved functional outcomes, but recovery in functional status over the three months did not contribute to HRQoL independently of attained functional status at three months.

This study has several strengths. First, the cohort of patients was of adequate size and its members were recruited with extremely high ascertainment and participation, and with minimal loss to follow-up over three months. Secondly, the instruments used to assess HRQoL – the DHP and the EQ-5D-3L – were official translations and had been used previously in Vietnamese populations. The validity of the DHP for use in the Vietnamese adolescent population had been tested [212] and, in preparation for this study, we had assessed its reliability and validity for use in this sample of stroke patients [377] (Chapter 6). Thirdly, assessment of HRQoL was available for almost all of the patients because caregivers had been used as proxy respondents for patients who had cognitive impairments or communication difficulties. Using proxy assessments can prevent exclusion of severely affected stroke patients from a study, and thereby avoid systematic bias from that source [378]. Fourthly, we established in the validation study that proxy assessments of HRQoL using the DHP and EQ-5D are as reliable and valid as assessments based on information provided by the patients in this cohort [377]. Whilst the proxy assessments for patients were a little lower on average than assessments by the patients themselves, we corrected for the difference in the analyses.

Our study also has some limitations. Firstly, because there is not a value set for the Vietnamese population with which to weigh responses to the EQ-5D, we used the value set for South Korea that is likely to approximately but not exactly reflect the preferences of Vietnamese people. Lacking normative data for the Vietnamese population, we were able

only to compare the mean utility score of a subset of the cohort (those aged over 60 years) with that of a similarly aged sample from a small rural community in northern Viet Nam. Secondly, the comparison of DHP scores of stroke patients to the general population was problematic because of the different sampling frame for the population sample. We corrected for differences in the age and sex distributions, but not for other factors such as socioeconomic status that may have differentiated the stroke patients. In addition, the population sample was drawn around 8 years earlier in 2004, and changes over the intervening period may have rendered as out-of-date the general population values. Thirdly, although depression was an important factor to predict poor HRQoL after stroke in many studies [227,237,357,379], we did not assess depression in our study. Finally, we established in the validation study that the DHP has only moderate reliability and validity for use with stroke patients [377] (Chapter 6). Part of the reason for this is that the DHP is a generic questionnaire that may underestimate the specific effects of stroke on HRQoL [227].

7.6. Conclusions

In conclusion, this first study of the HRQoL of survivors of stroke in Viet Nam, and one of the few to report longer term HRQoL from the developing world, has confirmed that stroke reduces the physical well-being of survivors with the most affected being those with the greatest impairment of functional status, and with greater reported deficits for women than men. The similarity of mean levels of HRQoL of survivors of stroke in this study with those of survivors in other countries, and in the factors associated with HRQoL, suggests that programs verified as being successful in improving the outcomes of stroke survivors in HICs can be considered for adoption in Viet Nam

7.7. Postscript

This chapter has reported findings in respect of the survivors at three months in a cohort of patients with first-ever stroke in Viet Nam. It completes the reporting of the outcomes of those survivors.

The next chapter (Chapter 8) summarises the work within this thesis and suggest the implications this may have for patients with stroke, public health professionals and health policy makers in Viet Nam.

Appendix 7: Additional findings on HRQoL of stroke on assessment of the DHP and the EuroQoL

Table A7.1: Mean scores of DHP physical health, DHP mental health and DHP social health in three-month survivors of stroke with adjustment for proxy response.

	Physical health (n=371)		Mental health (n=371)		Social health (n=369)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Age						
< 45 years	37	65.0 (55.6, 74.3)	37	68.3 (60.3, 76.3)	37	66.4 (62.0, 70.8)
45-54 years	92	55.7 (50.1, 61.3)	92	63.2 (58.2, 68.3)	92	57.1 (54.2, 60.0)
55-64 years	94	56.3 (50.7, 61.9)	95	67.4 (62.4, 72.4)	94	59.2 (56.4, 62.1)
65-74 years	74	42.5 (36.8, 48.2)	73	59.1 (53.5, 64.7)	74	55.3 (52.1, 58.5)
75+ years	74	38.9 (33.2, 44.5)	74	62.7 (57.0, 68.4)	73	56.8 (53.5, 60.1)
Trend		-6.3 **(-8.4, -4.2)***		-1.3 (-3.3, 0.7)		**-1.6 (-2.7, -0.4)***
Sex						
Male	200	57.3 (53.5, 61.2)	200	66.9 (63.4, 70.3)	200	58.8 (56.8, 60.8)
Female	171	43.1 (39.3, 46.9)	171	60.4 (56.8, 64.1)	170	57.3 (55.2, 59.5)
Difference		**-14.2 (-19.6, -8.8)***		**-6.4 (-11.4, -1.4)***		-1.5 (-4.4, 1.5)
Marital status						
Married	286	53.5 (50.3, 56.7)	285	65.3(62.5, 68.2)	286	59.2 (57.6, 60.8)
Single	17	59.8 (46.2, 73.3)	18	67.2 (55.9, 78.4)	17	56.3 (49.6, 63.1)
Divorced	6	52.4 (30.6, 74.2)	6	31.9 (13.6, 50.2)	6	60.3 (49.0, 71.6)
Widowhood(widower/widow)	62	35.4 (29.4, 41.3)	62	59.3 (53.3, 65.3)	61	53.2 (49.5, 56.8)
Wealth index						
1st quarter (richest)	91	54.0 (48.2, 59.9)	90	68.0 (62.9, 73.1)	90	60.4 (57.4, 63.3)
2nd quarter	79	49.4 (43.3, 55.5)	80	63.1 (57.7, 68.5)	79	56.7 (53.6, 59.9)
3rd quarter	96	50.6 (45.0, 56.2)	96	61.6 (56.7, 66.5)	96	55.9 (53.0, 58.7)
4th quarter (poorest)	99	48.0 (42.6, 53.5)	99	62.9 (58.0, 67.7)	99	59.9 (57.1, 62.7)
Trend		-1.7 (-4.2, 0.8)		-1.7 (-3.9, 0.5)		-0.2 (-1.5, 1.1)

	Physical health (n=371)		Mental health (n=371)		Social health (n=369)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Type of stroke						
ICH	89	50.2 (44.4, 55.9)	90	59.4 (54.3, 64.4)	89	56.7 (53.7, 59.7)
IS	282	50.6 (47.3, 53.9)	281	65.3 (62.5, 68.2)	281	58.6 (56.9, 60.2)
Difference		0.4 (-6.2, 7.1)		**5.9 (0.1, 11.7)**		1.9 (-1.5, 5.3)
Severity of impairment						
NIHSS ≤ 7	214	57.2 (53.4, 60.9)	212	68.2 (64.9, 71.4)	213	60.1 (58.2, 61.9)
NIHSS > 7	145	41.4 (37.2, 45.5)	147	59.0 (55.1, 62.8)	145	56.0 (53.7, 58.3)
Difference		**-15.8 (-21.4, -10.2)***		**-9.2 (-14.3, -4.2)***		**-4.1 (-7.1, -1.0)***
Disability at 3 month						
Least severe (mRS= 0/1)	126	72.9 (68.5, 77.2)	126	75.3 (71.3, 79.4)	126	65.2 (62.9, 67.5)
Least severe at admission	27	77.1 (67.7, 86.4)	27	80.1 (71.4, 88.8)	27	61.5 (56.6, 66.4)
Intermediate at admission	70	71.6 (65.9, 77.3)	70	75.1 (69.6, 80.5)	70	66.4 (63.4, 69.4)
Most severe at admission	29	72.7 (63.9, 81.6)	29	72.0 (63.7, 80.4)	29	66.0 (61.3, 70.6)
Intermediate (mRS=2/3)	141	49.0 (45.4, 52.6)	142	63.8 (60.1, 67.6)	140	57.1 (55.0, 59.3)
Least severe at admission	19	55.7 (45.6, 65.8)	19	60.5 (50.3, 70.7)	19	53.8 (47.8, 59.7)
Intermediate at admission	56	48.2 (42.6, 53.9)	55	63.4 (57.4, 69.4)	55	57.9 (54.4, 61.3)
Most severe at admission	64	49.0 (43.7, 54.2)	66	65.6 (60.1, 71.1)	64	58.1 (54.9, 61.3)
Most severe (mRS=4/5)	104	29.8 (26.1, 33.4)	103	50.7 (46.3, 55.1)	104	50.9 (48.3, 53.6)
Least severe at admission	0	n.a.	0	n.a.	0	n.a.
Intermediate at admission	31	32.8 (26.0, 39.5)	30	51.4 (43.3, 59.4)	31	50.6 (45.9, 55.3)
Most severe at admission	72	28.7 (24.4, 33.1)	72	49.9 (44.6, 55.1)	72	51.3 (48.2, 54.5)
Trend†		**-20.3 (-22.8, -12.7)***		**-12.2 (-15.2, -9.2)***		**-7.3 (-9.1, -5.5)***

*** idenotes p<0.05**

† Trend over three category means

Table A7.2: Means of DHP perceived health, DHP self-esteem and DHP anxiety scores of stroke survivors to three months at levels of study factors with adjustment for proxy response.

	Self-esteem (n=370)		Depression (n=371)		Anxiety (n=370)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Age						
< 45 years	37	81.7 (76.9, 86.6)	37	72.3 (64.8, 79.7)	37	78.6 (73.0, 84.2)
45-54 years	92	76.2 (72.9, 79.5)	92	67.1 (62.3, 71.9)	92	73.2 (69.5, 76.9)
55-64 years	95	78.2 (75.0, 81.3)	94	70.2 (65.5, 74.9)	94	76.3 (72.7, 79.9)
65-74 years	73	75.3 (71.5, 79.1)	74	63.5 (58.2, 68.8)	74	72.0 (67.8, 76.2)
75+ years	73	77.9 (74.2, 81.6)	74	63.0 (57.6, 68.5)	73	73.4 (69.1, 77.6)
Trend		-0.5 (-1.8, 0.8)		**-2.0 (-3.9, -0.1)***		-0.9 (-2.4, 0.6)
Sex						
Male	200	78.3 (76.1, 80.4)	200	70.8 (67.6, 74.0)	200	76.0 (73.5, 78.4)
Female	170	76.4 (74.0, 78.9)	171	62.3 (58.8, 65.7)	170	72.4 (69.7, 75.2)
Difference		**-1.8 (-5.1, 1.5)***		**-8.5 (-13.2, -3.8)***		-3.6 (-7.2, 0.1)
Marital status						
Married	285	78.2 (76.4, 80.0)	286	68.8 (66.1, 71.4)	286	75.6 (73.5, 77.6)
Single	18	79.9 (72.8, 87.0)	17	73.7 (62.9, 84.5)	17	78.8 (70.6, 86.9)
Divorced	6	64.3 (49.0, 79.6)	6	44.5 (25.4, 63.6)	6	64.9 (49.3, 80.4)
Widowhood(widower/widow)	61	74.0 (69.8, 78.2)	62	58.5 (52.7, 64.3)	61	68.0 (63.2, 72.7)
Wealth index						
1st quarter (richest)	90	79.2 (75.9, 82.4)	91	70.0 (65.2, 74.8)	90	76.2 (72.5, 79.8)
2nd quarter	79	77.5 (74.0, 81.0)	79	65.6 (60.5, 70.8)	79	72.4 (68.3, 76.4)
3rd quarter	96	75.4 (72.1, 78.7)	96	65.5 (60.8, 70.2)	96	72.1 (68.4, 75.7)
4th quarter (poorest)	99	77.9 (74.8, 81.1)	99	66.2 (61.6, 70.9)	99	76.3 (72.8, 79.8)
Trend		-0.6 (-2.0, 0.9)		-1.2 (-3.3, 1.0)		0 (-1.6, 1.7)

	Self-esteem (n=370)		Depression (n=371)		Anxiety (n=370)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Type of stroke						
ICH	89	75.2 (71.8, 78.6)	89	64.3 (59.4, 69.2)	89	73.7 (69.9, 77.4)
IS	281	78.1 (76.3, 80.0)	282	67.7 (65.0, 70.4)	281	74.6 (72.5, 76.7)
Difference		2.9 (-1.0, 6.8)		3.4 (-2.2, 9.0)		0.9 (-3.4, 5.2)
Severity of impairment						
NIHSS≤ 7	212	80.2 (78.2, 82.2)	214	71.1 (68.0, 74.1)	213	76.8 (74.4, 79.1)
NIHSS> 7	146	74.2 (71.5, 76.8)	145	61.5 (57.7, 65.2)	145	71.0 (68.0, 74.0)
Difference		**-6.0 (-9.4, -2.7)***		**-9.6 (-14.5, -4.7)***		**-5.8 (-9.6, -1.9)***
Disability at 3 month						
Least severe (mRS= 0/1)	126	85.0 (82.6, 87.4)	126	78.6 (74.9, 82.3)	126	82.2 (79.4, 85.0)
Least severe at admission	27	85.6 (80.6, 90.6)	27	82.0 (74.2, 89.9)	27	83.2 (77.3, 89.1)
Intermediate at admission	70	84.9 (81.7, 88.0)	70	78.4 (73.5, 83.4)	70	81.9 (76.1, 87.7)
Most severe at admission	29	85.1 (80.2, 89.9)	29	76.1 (68.4, 83.8)	29	73.3 (65.6, 80.9)
Intermediate (mRS=2/3)	142	76.0 (73.6, 78.5)	141	66.6 (63.1, 70.1)	140	73.5 (70.6, 76.3)
Least severe at admission	19	72.8 (65.7, 79.9)	19	67.2 (57.7, 76.8)	19	72.4 (67.9, 76.9)
Intermediate at admission	55	77.1 (73.2, 81.0)	56	66.1 (60.5, 71.7)	55	75.2 (71.1, 79.3)
Most severe at admission	66	76.5 (72.8, 80.1)	64	67.4 (62.2, 72.7)	64	66.5 (60.1, 72.9)
Most severe (mRS=4/5)	102	69.4 (66.1, 72.7)	104	53.5 (49.2, 57.8)	104	65.6 (62.0, 69.1)
Least severe at admission	0	n.a.	0	n.a.	0	n.a.
Intermediate at admission	30	70.6 (64.8, 76.4)	31	55.3 (47.6, 63.0)	31	66.5 (60.1, 72.9)
Most severe at admission	71	69.2 (65.2, 73.1)	72	52.2 (47.0, 57.4)	72	65.0 (60.7, 69.4)
Trend†		**-8.3 (-10.5, -6.1)***		**-3.7 (-4.5, -2.8)***		**-8.6 (-11.1, -6.2)***

*denotes $p<0.05$

† Trend over three category means

Table A7.3: Means of DHP perceived health, DHP pain and DHP disability of stroke survivors to three months at levels of study factors with adjustment for proxy response.

	Perceived health (n=369)		Pain (n=371)		Disability (n=372)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Age						
<45 years	37	37.2 (25.7, 48.7)	37	72.6 (61.2, 83.9)	37	84.5 (70.9, 98.1)
45-54 years	92	32.5 (25.1, 39.8)	92	66.4 (59.2, 73.6)	92	74.9 (66.2, 83.5)
55-64 years	93	30.7 (23.4, 38.0)	94	71.2 (64.1, 78.4)	95	72.8 (64.3, 81.4)
65-74 years	73	25.8 (17.7, 34.0)	74	57.0 (49.0, 65.1)	74	60.6 (50.9, 70.2)
75+ years	74	20.2 (11.9, 28.5)	74	53.2 (45.1, 61.4)	74	57.2 (47.4, 67.0)
Trend		**-4.1 (-7.0, -1.2)***		**-4.8 (-7.7, -2.0)***		**-6.7 (-10.2, -3.3)***
Sex						
Male	200	31.9 (26.9, 36.8)	200	69.9 (65.0, 74.7)	200	69.3 (63.4, 75.3)
Female	169	25.0 (19.6, 30.4)	171	56.6 (51.3, 61.8)	172	68.5 (62.1, 74.9)
Difference		-6.9 (-14.2, 0.4)		**-13.3 (-20.5, -6.1)***		-0.8 (-9.6, 7.9)
Marital status						
Married	285	29.8 (25.7, 34.0)	286	65.9 (61.9, 70.0)	286	69.3 (64.4, 74.3)
Single	18	42.3 (25.8, 58.8)	17	80.0 (63.4, 96.6)	18	78.5 (58.7, 98.3)
Divorced	6	22.9 (-5.7, 51.5)	6	81.8 (53.9, 109.8)	6	47.6 (13.3, 82.0)
Widowhood(widower/widow)	60	20.1 (11.0, 29.1)	62	47.5 (38.8, 56.2)	62	66.5 (55.8, 77.2)
Wealth index						
1st quarter (richest)	90	35.1 (27.7, 42.6)	91	63.6 (56.3, 71.0)	92	73.4 (64.6, 82.2)
2nd quarter	78	30.6 (22.6, 38.5)	79	63.1 (55.2, 71.0)	79	62.6 (53.2, 72.1)
3rd quarter	96	25.4 (18.3, 32.6)	96	64.0 (56.8, 71.1)	96	70.2 (61.6, 78.8)
4th quarter (poorest)	99	24.9 (17.8, 32.0)	99	64.0 (56.9, 71.0)	99	67.8 (59.3, 76.3)
Trend		**-3.6 (-6.8, -0.3)**		0.2 (-3.0, 3.4)		-1.0 (-4.9,2.9)

	Perceived health (n=369)		Pain (n=371)		Disability (n=372)	
	Num	Mean (95% CI)	Num	Mean (95% CI)	Num	Mean (95% CI)
Type of stroke						
ICH	90	29.2 (21.7, 36.6)	89	59.9 (52.5, 67.3)	90	61.9 (53.1, 70.7)
IS	279	28.6 (24.4, 32.8)	282	65.0 (60.8, 69.1)	282	71.2 (66.2, 76.2)
Difference		-0.6 (-9.1, 7.9)		5.1 (-3.4, 13.6)		9.3 (-0.8, 19.5)
Severity of impairment						
NIHSS ≤ 7	211	34.2 (29.4, 39.0)	214	69.0 (64.2, 73.7)	214	76.7 (71.1, 82.3)
NIHSS > 7	146	21.4 (15.6, 27.2)	145	55.8 (50.0, 61.6)	146	59.8 (53.0, 66.6)
Difference		**-12.8 (-20.4, -5.2)***		**-13.1 (-20.7, -5.6)***		**-17.0 (-25.8, -8.1)***
Disability at 3 month						
Least severe (mRS= 0/1)	126	46.0 (40.0, 51.9)	126	76.9 (70.9, 82.9)	126	94.1 (88.1, 100.1)
Least severe at admission	27	47.7 (34.9, 60.6)	27	79.4 (66.7, 92.1)	27	96.4 (83.7, 109.1)
Intermediate at admission	70	47.7 (39.6, 55.7)	70	73.1 (65.2, 81.1)	70	93.8 (85.8, 101.8)
Most severe at admission	29	40.6 (28.2, 53.0)	29	84.1 (71.9, 96.4)	29	93.3 (81.0, 105.6)
Intermediate (mRS=2/3)	141	20.6 (15.0, 26.1)	141	63.9 (58.2, 69.5)	142	77.1 (71.5, 82.7)
Least severe at admission	18	24.0 (8.2, 39.7)	19	76.0 (60.9, 91.2)	19	79.1 (63.9, 94.3)
Intermediate at admission	55	22.1 (13.1, 31.1)	56	59.9 (51.1, 68.8)	56	75.8 (67.0, 84.7)
Most severe at admission	66	18.1 (10.0, 26.3)	64	64.8 (56.6, 73.1)	65	80.0 (71.8, 88.2)
Most severe (mRS=4/5)	102	18.7 (12.0, 25.4)	104	47.7 (41.0, 54.3)	104	27.3 (20.7, 34.0)
Least severe at admission	0	n.a.	0	n.a.	0	n.a.
Intermediate at admission	30	23.7 (11.5, 35.8)	31	59.8 (48.0, 71.6)	31	30.6 (18.7, 42.4)
Most severe at admission	72	16.5 (8.5, 24.5)	72	42.9 (35.0, 50.9)	72	26.0 (18.1, 34.0)
Trend†		**-14.1 (-18.7, -9.5)***		**-14.5 (-19.1, -10.0)***		**-32.8 (-37.4, -28.1)***

*denotes $p<0.05$

† Trend over three category means

Table A7.4: Mean score of DHP of all patients and population (after age and sex standardisation).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	60.1	60.1	0.04	1.0	53.5	45.7	-57.8	0.57
Mental health	74.0	67.5	-6.5	0.66	72.7	60.8	-11.9	0.39
Social health	57.7	58.5	0.8	0.94	52.8	56.8	4.0	0.61
General health	63.9	62.2	-1.7	0.88	59.7	54.5	-5.2	0.58
Perceived health	56.0	32.0	-24.0	0.30	48.3	24.9	-21.9	0.22
Self-esteem	73.3	76.3	11.2	0.79	69.9	73.7	3.9	0.72
Anxiety	69.1	74.5	3.0	0.79	67.7	70.3	2.6	0.82
Depression	66.7	70.6	3.9	0.79	61.4	61.6	0.2	0.99
Pain	54.0	70.0	16.0	0.45	53.7	56.4	2.8	0.89
Disability	97.4	69.5	-25.2	0.30	95.0	68.3	-26.7	0.26

Table A7.5: Mean score of DHP of least severe (mRS=0/1) at three months patients and population (after age and sex standardisarion).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	63.7	79.4	15.7	P=0.07	55.9	66.1	10.1	P=0.15
Mental health	73.7	76.0	2.4	P=0.81	70.4	77.7	7.2	P=0.16
Social health	59.0	65.4	6.4	P=0.30	**54.3**	**66.3**	**12.0**	**P<0.001**
General health	65.5	73.6	8.2	P=0.18	**60.2**	**70.0**	**9.8**	**P=0.005**
Perceived health	58.2	50.0	-8.2	P=0.63	49.8	40.7	-9.1	P=0.44
Self-esteem	73.4	83.3	9.8	P=0.13	**69.8**	**87.4**	**17.7**	**P<0.001**
Anxiety	70.0	81.6	11.7	P=0.12	**67.2**	**82.8**	**15.6**	**P=0.003**
Depression	68.5	79.8	11.3	P=0.23	**61.8**	**77.9**	**16.1**	**P=0.02**
Pain	58.0	82.5	24.6	P=0.07	54.1	67.4	13.3	P=0.16
Disability	98.0	94.0	P=-4.0	P=0.66	95.0	94.2	-0.8	P=0.87

Table A7.6: Mean score of DHP of intermediate severe (mRS=2/3) at three months patients and population (after age and sex standardisation).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	60.5	55.0	-5.5	P=0.50	54.3	45.6	-8.6	P=0.28
Mental health	73.9	65.9	-8.0	P=0.44	71.3	62.3	-9.1	P=0.30
Social health	58.2	56.3	-1.9	P=0.78	53.5	57.0	3.5	P=0.53
General health	64.2	59.1	-5.1	P=0.41	59.7	55.1	-4.6	P=0.40
Perceived health	**56.4**	**22.5**	**-33.9**	**P=0.02**	**49.0**	**18.6**	**-30.4**	**P=0.01**
Self-esteem	73.5	73.7	0.1	P=0.99	69.7	73.1	3.5	P=0.66
Anxiety	69.3	72.9	3.6	P=0.65	67.3	70.7	3.4	P=0.63
Depression	67.0	69.1	2.2	P=0.82	61.2	63.0	1.8	P=0.84
Pain	54.4	69.3	14.9	P=0.27	53.6	58.5	4.8	P=0.73
Disability	97.2	72.1	P=-25.1	P=0.15	94.9	81.9	-12.9	P=0.32

Table A7.7: Mean score of DHP of most severe (mRS=4/5) at three months patients and population (after age and sex standardisation).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	**52.9**	**33.6**	**-19.3**	**P=0.04**	**50.6**	**30.4**	**-20.2**	P=0.007
Mental health	**74.6**	**54.4**	**-20.3**	**P=0.04**	**76.2**	**46.3**	**-29.9**	P=0.001
Social health	54.9	49.6	-5.3	P=0.45	50.9	49.5	-1.5	P=0.76
General health	**60.8**	**46.5**	**-14.3**	**P=0.03**	**59.2**	**42.1**	**-17.2**	**P=0.002**
Perceived health	**51.4**	**14.1**	**-37.2**	**P=0.002**	**46.2**	**20.5**	**-25.6**	**P=0.03**
Self-esteem	72.7	67.6	-5.1	P=0.56	70.2	63.9	-6.3	P=0.33
Anxiety	67.3	64.2	-3.1	P=0.56	68.5	60.2	-8.3	P=0.25
Depression	63.4	56.6	-6.8	P=0.49	61.3	47.5	-13.8	P=0.10
Pain	46.4	48.9	2.6	P=0.87	53.4	45.6	-7.8	P=0.56
Disability	**96.5**	**22.3**	**16.9**	**P<0.001**	**95.2**	**31.6**	**-63.6**	**P<0.001**

Table A7.8: Mean score of DHP of least severe (mRS=0/1) at admission patients and population (after age and sex standardisation).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	62.4	79.4	17.0	P=0.05	55.9	66.1	10.2	P=0.15
Mental health	73.5	76.0	2.6	P=0.80	71.0	77.7	6.7	P=0.19
Social health	58.7	65.4	6.8	P=0.28	54.7	66.3	11.6	**P<0.001**
General health	64.8	73.6	8.8	P=0.15	60.5	70.0	9.5	**P=0.01**
Perceived health	57.2	50.0	16.9	P=0.67	49.2	40.7	-8.5	P=0.48
Self-esteem	73.2	83.3	10.1	P=0.12	70.4	87.4	17.1	**P<0.001**
Anxiety	70.1	81.6	11.5	P=0.13	67.7	82.8	15.1	**P<0.001**
Depression	67.8	79.8	12.0	P= 0.20	62.1	77.9	15.8	**P=0.02**
Pain	55.9	82.5	26.6	P=0.05	53.7	67.4	13.7	P=0.15
Disability	97.4	94.0	-3.4	P=0.71	95.4	94.2	-1.2	P=0.81

Table A7.9: Mean score of DHP of intermediate (mRS=2/3) at admission patients and population (after age and sex standardisation).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	60.4	63.6	3.2	P=0.79	53.1	49.0	-4.1	P=0.64
Mental health	74.0	67.1	-7.0	P=0.58	71.8	66.9	-4.9	P=0.56
Social health	58.0	60.2	2.3	P=0.79	52.7	59.9	7.2	P=0.14
General health	64.1	64.1	0	P=1.0	59.2	58.5	-0.7	P=0.91
Perceived health	56.2	36.9	-19.3	P=0.28	48.4	30.6	-17.8	P=0.16
Self-esteem	73.5	76.7	3.3	P=0.71	69.3	78.7	9.4	P=0.16
Anxiety	69.0	74.9	5.9	P=0.51	67.1	73.8	6.6	P=0.37
Depression	66.9	71.1	4.2	P=0.68	60.6	67.1	6.5	P=0.45
Pain	54.5	71.4	16.9	P=0.28	53.3	58.8	5.5	P=0.69
Disability	97.5	74.2	-22.8	P=0.24	94.6	75.0	-19.6	P=0.19

Table A 7.10: Mean score of DHP of most severe (mRS=4/5) at admission patients and population (after age and sex standardisation).

	Males				Females			
	Population	All stroke	Difference	p-value	Population	All stroke	Difference	p-value
Physical health	58.9	53.1	-5.9	p=0.63	53.1	38.6	-14.5	P=0.15
Mental health	74.1	65.5	-8.6	p=0.39	74.1	53.8	-20.3	P=0.06
Social health	57.2	57.9	0.7	p=0.92	52.4	53.6	1.3	P=0.83
General health	63.4	58.9	-4.5	p=0.57	59.9	48.8	-11.0	P=0.12
Perceived health	55.3	23.8	-31.4	P=0.06	47.9	17.9	-30.0	**P=0.03**
Self-esteem	73.2	75.7	2.5	P=0.76	70.2	68.5	-1.7	P=0.83
Anxiety	68.8	72.8	4.0	P=0.66	68.1	66.2	-1.9	P=0.83
Depression	66.2	67.3	1.1	P=0.92	61.9	54.9	-7.0	P=0.51
Pain	52.8	65.9	13.1	P=0.43	54.0	50.6	-3.4	P=0.82
Disability	97.2	60.0	-37.2	P=0.08	95.2	58.0	-37.2	**P=0.05**

Table A7.11: Comparison EQ-5D utility score between patients with stroke and the aging general population (FilaBavi).

Aging general population (60+ years)	0.88 (95% CI 0.87, 0.88)
All 60+ years patients (unweighted)	0.57 (SD 0.36)
All 60+ years patients (weighted)	0.58 (SD 0.35)
Patients with less severe disability (mRS=0/1) at 3 months	0.95 (SD 0.08)
Patients with less severe disability (mRS=2/3) at 3 months	0.71 (SD 0.13)
Patients with less severe disability (mRS=4/5) at 3 months	0.25 (SD 0.27)
All 60+ years patients (weighted)	
Patients with less severe disability (mRS=0/1) at admission	0.82 (SD 0.15)
Patients with less severe disability (mRS=2/3) at admission	0.69 (SD 0.31)
Patients with less severe disability (mRS=4/5) at admission	0.45 (SD 0.35)

Table A7.12: Means and difference of means of DHP physical health, DHP mental health and DHP social health scores of stroke survivors to three months at levels of study factors with adjustment for age, sex, proxy response , severity of stroke at admission and disability at three months

	DHP physical health		DHP mental health		DHP social health	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Age						
< 45 years	66.8(57.9, 75.7)	56.6(49.4, 63.8)	70.1(62.2, 77.8)	64.2(56.8, 71.5)	67.7(63.3, 72.1)	64.5(60.2, 68.8)
45-54 years	**-12.6(-23.0, -2.3)**	-5.3(-13.6, 2.9)	-7.0(-16.2, 2.1)	-2.8(-11.4, 5.7)	**-10.2(-15.5, -5.0)**	**-8.1(-13.1, -3.1)**
55-64 years	**-11.6(-21.9, -1.3)**	-2.8(-11.2, 5.5)	-2.6(-11.8, 6.5)	2.4(-6.2, 11.0)	**-8.5(-13.8, -3.3)**	**-5.8(-10.9, -0.8)**
65-74 years	**-24.7(-35.2, -14.3)**	**-9.0(-17.8, -0.2)**	**-10.8(-20.3, -1.2)**	-1.4(-10.6, 7.9)	**-12.2(-17.7, -6.7)**	**-7.1(-12.5, -1.7)**
75+ years	**-24.5(-35.2, -13.8)**	-8.4(-17.5, 0.6)	-5.6(-15.3, 4.2)	3.8(-5.5, 13.2)	**-10.7(-16.3, -5.1)**	**-5.6(-11.1, -0.1)**
Trend	**-5.5(-7.6, -3.5)**	-1.8(-3.6, 0.1)	-1.1(-3.1, 0.9)	1.2(-0.7, 3.2)	**-1.8(-3.0, -0.6)**	-0.5(-1.6, 0.7)
Sex						
Male	55.6(51.9, 59.2)	54.5(51.5, 57.5)	66.7(63.3, 70.1)	65.9(62.8, 69.0)	58.4(56.5, 60.4)	58.0(56.1, 59.9)
Female	**-10.4(-15.6, -5.1)**	**-7.4(-11.8, -3.0)**	-4.9(-10.0, 0.1)	-2.9(-7.6, 1.8)	0(-2.9, 3.0)	1.1(-1.8, 3.9)
Marital status						
Married	51.4(48.4, 54.4)	51.5(49.0, 53.9)	64.7(61.9, 67.5)	64.8(62.2, 67.4)	59.1(57.4, 60.8)	59.0(57.5, 60.6)
Single	10.3(-3.4, 24.1)	10.8(-0.5, 22.1)	5.0(-6.9, 16.8)	4.9(-6.1, 15.8)	-1.7(-9.0, 5.5)	-1.6(-8.4, 5.3)
Divorced	-1.2(-21.2, 18.8)	0.7(-16.1, 17.4)	**-33.3(-51.4, -15.2)**	**-32.0(-49.1, -14.9)**	0.4(-10.8, 11.7)	1.1(-9.5, 11.7)
Widowhood	-6.4(-14.4, 1.6)	-5.3(-12.0, 1.3)	0.5(-7.2, 8.2)	0.9(-6.2, 8.0)	-3.7(-8.4, 0.9)	-3.4(-7.8, 1.0)
Wealth index †						
1st quarter (richest)	55.8(50.4, 61.2)	51.9(47.5, 56.4)	70.1(65.2, 75.1)	67.5(62.9, 72.2)	61.5(58.7, 64.4)	60.1(57.4, 62.9)
2nd quarter	-6.9(-14.7, 0.9)	-0.4(-7.0, 6.1)	-7.0(-14.2, 0.3)	-2.8(-9.7, 4.0)	**-4.8(-9.1, -0.6)**	-2.6(-6.7, 1.5)
3rd quarter	-6.3(-13.6, 1.1)	-0.7(-6.9, 5.5)	**-8.8(-15.7, -1.9)**	-5.0(-11.5, 1.5)	**-5.7(-9.7, -1.6)**	-3.8(-7.6, 0.1)
4th quarter (poorest)	-7.0(-14.4, 0.3)	-2.3(-8.5, 3.8)	**-7.1(-14.0, -0.2)**	-4.0(-10.4, 2.5)	-1.5(-5.5, 2.5)	0.1(-3.7, 4.0)
Trend	**-2.0(-4.3, 0.2)**	-0.7(-2.7, 1.2)	**-2.3(-4.5, -0.1)**	-1.4(-3.4, 0.7)	-0.5(-1.8, 0.8)	-0.1(-1.3, 1.2)

	DHP physical health		DHP mental health		DHP social health	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Type of stroke						
ICH	51.1(45.3, 56.9)	52.1(47.3, 57.0)	61.9(56.4, 67.4)	62.7(57.6, 67.7)	57.8(54.6, 61.1)	58.1(55.1, 61.2)
IS	-0.5(-7.2, 6.2)	-1.4(-7.0, 4.1)	3.2(-3.1, 9.5)	2.5(-3.4, 8.3)	0.8(-2.9, 4.5)	0.4(-3.1, 4.0)
Severity of impairment						
NIHSS ≤ 7	56.7(53.2, 60.2)	51.3(48.4, 54.2)	68.0(64.8, 71.2)	64.5(61.4, 67.6)	60.0(58.1, 61.8)	58.1(56.2, 59.9)
NIHSS > 7	**-14.5(-19.7, -9.3)**	-0.7(-5.6, 4.2)	**-8.8(-13.9, -3.8)**	0.3(-4.9, 5.5)	**-3.8(-6.8, -0.8)**	1.0(-2.1, 4.1)
Disability						
Least severe (mRS=0/1)	61.5(53.3, 69.7)	56.1(49.5, 62.8)	67.1(59.7, 74.6)	63.8(56.8, 70.7)	56.3(51.9, 60.6)	54.3(50.1, 58.5)
Intermediate (mRS=2/3)	**-10.2(-18.9, -1.5)**	-5.0(-12.1, 2.1)	-3.0(-11.0, 5.0)	0.2(-7.3, 7.6)	3.2(-1.5, 7.9)	5.0(0.5, 9.4)
More severe (mRS=4/5)	**-13.7(-23.6, -3.8)**	-6.0(-14.2, 2.2)	-3.5(-12.7, 5.8)	1.4(-7.2, 10.0)	2.1(-3.3, 7.5)	4.8(-0.3, 10.0)
Trend	**-5.9(-10.4, -1.5)**	-2.5(-6.4, 1.3)	-1.5(-5.9, 3.0)	0.8(-3.4, 5.0)	0.6(-2.0, 3.2)	1.9(-0.6, 4.3)
Disability at 3 months						
Least severe (mRS=0/1)	70.4(65.9, 75.0)	n.n.	74.9(70.5, 79.2)	n.n.	65.6(63.1, 68.1)	n.n.
Intermediate (mRS=2/3)	**-20.8(-26.5, -15.0)**		**-9.9(-15.6, -4.1)**		**-8.0(-11.3, -4.7)**	
More severe (mRS=4/5)	**-39.2(-46.0, -32.5)**		**-23.8(-31.1, -16.5)**		**-14.9(-19.2, -10.6)**	
Trend	**-18.6(-21.6, -15.6)**		**-11.7(-15.3, -8.1)**		**-7.6(-9.8, -5.4)**	

* Adjusted for age, sex, proxy response and severity of impairment at admission

Table A7.13: Means and difference of means of DHP self-esteem, DHP anxiety and DHP depression scores of stroke survivors to three months at levels of study factors with adjustment for age, sex, proxy response , severity of stroke at admission and disability at three months

	DHP self-esteem		DHP anxiety		DHP depression	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Age						
< 45 years	82.9(78.1, 87.6)	79.6(74.8, 84.4)	79.7(74.1, 85.2)	75.3(69.8, 80.8)	73.6(66.4, 80.9)	67.4(60.5, 74.2)
45-54 years	**-6.6(-12.4, -0.9)**	-4.4(-10.1, 1.3)	-6.5(-13.2, 0.1)	-3.6(-10.0, 2.9)	-7.2(-15.8, 1.4)	-2.8(-10.8, 5.2)
55-64 years	-4.7(-10.4, 1.0)	-1.9(-7.6, 3.7)	-3.6(-10.2, 3.0)	0.1(-6.3, 6.5)	-3.5(-12.1, 5.1)	1.9(-6.1, 9.9)
65-74 years	**-7.1(-13.1, -1.0)**	-1.7(-7.8, 4.3)	**-8.0(-14.9, -1.0)**	-0.9(-7.8, 6.0)	**-10.4(-19.4, -1.4)**	-0.2(-8.8, 8.3)
75+ years	-4.4(-10.5, 1.7)	0.9(-85.2, 6.9)	-5.6(-12.7, 1.5)	1.4(-5.6, 8.4)	-8.6(-17.8, 0.6)	1.6(-7.1, 10.3)
Trend	-0.5(-1.8, 0.8)	0.8(-0.5, 2.1)	-0.9(-2.4, 0.6)	0.9(-0.6, 2.3)	-1.7(-3.6, 0.2)	0.8(-1.0, 2.7)
Sex						
Male	78.3(76.1, 80.4)	77.8 (75.7, 79.9)	75.8(73.3, 78.3)	75.2(72.9, 77.6)	70.5(67.3, 73.6)	69.8(66.9, 72.7)
Female	-1.0(-4.3, 2.3)	0.2(-2.9, 3.4)	-2.8(-6.6, 0.9)	-1.4(-5.0, 2.1)	**-7.1(-11.9, -2.4)**	**-5.1 (-9.5, -0.8)**
Marital status						
Married	78.3(76.4, 80.1)	78.3(76.5, 40.0)	75.3(73.2, 77.4)	75.3(73.4, 77.3)	67.9(65.3, 70.6)	68.0(65.6, 70.4)
Single	3.0(-4.5, 10.4)	2.9(-4.1, 10.0)	5.1(-3.6, 13.8)	5.3 (-2.8, 13.4)	8.1(-3.2, 19.5)	8.4 (-1.8, 18.7)
Divorced	-14.5(-29.8, 0.9)	-13.6(-27.9, 0.8)	-10.8(-26.3, 4.7)	-9.9(-24.3, 4.5)	**-24.2(-42.8, -5.6)**	-23.1(-40.2, -5.9)
Widowhood	-2.4(-7.6, 2.8)	-2.2(-7.1, 2.8)	-5.5(-11.5, 0.5)	-5.0(-10.6, 0.6)	-4.0(-11.3, 3.4)	-3.3 (-10.0, 3.4)
Wealth index †						
1st quarter (richest)	80.5(77.3, 83.6)	78.9(75.9, 82.0)	77.1(73.4, 80.7)	75.3(71.8, 78.8)	71.4(66.8, 76.1)	69.0(64.7, 73.3)
2nd quarter	-3.0(-7.7, 1.7)	-0.6(-5.1, 4.0)	-4.6(-10.1, 0.8)	-1.6 (-6.8, 3.6)	-5.6(-12.5, 1.3)	-1.4(-7.8, 5.0)
3rd quarter	**-4.9(-9.5, -0.4)**	-2.7(-7.1, 1.6)	**-5.8(-11.0, -0.6)**	-3.2(-8.1, 1.7)	**-6.7(-13.2, -0.2)**	-3.1(-9.2, 2.9)
4th quarter (poorest)	-2.5(-6.9, 2.0)	-0.6(-4.9, 3.7)	-0.6(-5.7, 4.5)	1.6(-3.2, 6.4)	-4.8(-11.3, 1.7)	-1.8(-7.8, 4.2)
Trend	-1.0(-2.4, 0.5)	-0.4(-1.8, 1.00	-0.3(-1.9, 1.4)	0.3(-1.2, 1.9)	-1.6(-3.6, 0.5)	-0.7(-2.6, 1.2)

	DHP self-esteem		DHP anxiety		DHP depression	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Type of stroke						
ICH	77.3(73.6, 80.9)	77.6(74.2, 81.1)	75.2(71.1, 79.7)	75.7(71.9, 79.5)	66.3(61.1, 71.5)	67.0(62.3, 71.8)
IS	0.7(-3.5, 4.9)	0.3(-3.6, 4.2)	-0.9(-5.6, 3.8)	-1.4(-5.8, 3.0)	1.2(-4.8, 7.2)	0.5(-5.0, 6.0)
Severity of impairment						
NIHSS≤ 7	80.1(78.1, 82.2)	78.1(76.1, 80.2)	76.7(74.3, 79.0)	74.2(71.9, 76.5)	70.8(67.8, 73.8)	67.0(62.3, 71.8)
NIHSS> 7	**-5.9(-9.3, -2.5)**	-0.7(-4.2, 2.8)	**-5.5(-9.3, -1.7)**	0.9(-3.0, 4.8)	**-9.0(-13.8, -4.2)**	0.5(-5.0, 6.0)
Disability						
Least severe (mRS=0/1)	77.9(73.0, 82.8)	75.9(71.1, 80.7)	76.9(71.5, 82.4)	74.5(69.3, 79.7)	71.9(64.9, 78.8)	68.5(62.0, 74.9)
Intermediate (mRS=2/3)	0.4(-4.8, 5.7)	2.3(-2.8, 7.4)	-2.4(-8.2, 3.5)	0(-5.6, 5.6)	-4.5(-12.0, 3.0)	-1.3(-8.2, 5.6)
More severe (mRS=4/5)	-0.5(-6.5, 5.5)	2.4(-3.5, 87.2)	-3.1(-9.9, 3.7)	0.4(-6.0, 6.9)	-6.3(-14.9, 2.4)	-1.2(-9.2, 6.8)
Trend	-0.4(-3.3, 2.6)	0.9(-1.8, 3.7)	-1.4(-4.8, 2.0)	0.3(-2.8, 3.4)	-7.6(-18.0, 2.9)	-0.5(-4.4, 3.4)
Disability at 3 months						
Least severe (mRS=0/1)	85.2(82.6, 87.8)	n.n.	82.6(79.6, 85.7)	n.n.	78.0(74.0, 82.0)	n.n.
Intermediate (mRS=2/3)	**-8.6(-12.2, -5.0)**		**-8.4(-12.6, -4.3)**		**-10.4(-15.7, -5.1)**	
More severe (mRS=4/5)	**-16.0(-20.9, -11.0)**		**-18.4(-24.0, -12.8)**		**-24.4(-31.3, -17.5)**	
Trend	**-8.5(-11.2, -5.8)**		**-9.5(-12.4, -6.5)**		**-12.2(-15.6, -8.7)**	

* Adjusted for age, sex, proxy response and severity of impairment at admission

Table A7.14: Means and difference of means of DHP perceived health, DHP pain and DHP disability scores of stroke survivors to three months at levels of study factors with adjustment for age, sex, proxy response , severity of stroke at admission and disability at three months

	DHP perceived health		DHP pain		DHP disability	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Age						
< 45 years	38.3(26.7, 50.0)	31.3(19.8, 42.8)	72.9.(61.6, 84.2)	67.1(55.8, 78.4)	89.5(76.2, 102.7)	73.2(61.8, 84.5)
45-54 years	-6.0(-19.8, 7.7)	-1.1(-14.5, 12.2)	-8.0(-21.4, 5.3)	-4.1(-17.2, 9.0)	-13.4(-29.0, 2.3)	-2.3(-15.5, 10.8)
55-64 years	-8.4(-22.2, 5.4)	-2.7(-16.1, 10.7)	-3.3(-16.6, 10.1)	1.6(-11.6, 14.7)	**-17.6(-33.2, -2.0)**	-4.2(-17.4, 8.9)
65-74 years	-11.6(-26.0, 2.8)	-0.6(-15.0, 13.8)	**-16.2(-30.1, -2.3)**	-7.3(-21.4, 6.9)	**-27.7(-44.0, -11.5)**	-2.4(-16.6, 11.8)
75+ years	**-17.0(-31.7, -2.4)**	-6.0(-20.6, 8.7)	**-16.1(-30.3, -1.9)**	-7.0(-21.4, 7.4)	**-31.6(-48.3, -15.0)**	-6.0(-20.4, 8.5)
Trend	**-3.8(-6.8, -0.8)**	-1.2(-4.2, 1.9)	**-3.8(-6.8, -0.9)**	-1.6(-4.6, 1.4)	**-7.4(-10.8, -3.9)**	-1.1(-4.1, 1.9)
Sex						
Male	30.8(25.7, 35.8)	29.8(24.9, 34.6)	68.5(63.6, 73.4)	67.7(62.9, 72.5)	67.2(61.5, 73.0)	65.0(60.3, 69.8)
Female	-3.9(-11.5, 3.7)	-1.7 (-9.0, 5.6)	**-10.6(-18.0, -3.2)**	**-8.8 (-16.0, -1.6)**	5.7(-2.9, 14.3)	10.5(3.3, 17.6)
Marital status						
Married	28.6(24.3, 32.7)	28.6(24.5, 32.7)	64.1 (59.9, 68.2)	63.9(59.9, 67.9)	68.0(63.1, 72.8)	67.7(63.6, 71.6)
Single	14.9(-3.0, 32.8)	14.7(-2.5, 31.9)	16.1(-1.7, 33.9)	16.4(-0.9, 33.8)	11.6(-8.6, 31.8)	11.2(-5.6, 28.0)
Divorced	-7.5(-36.1, 21.1)	-6.1 (-33.6, 21.5)	16.4(-11.3, 44.1)	17.5(-9.4, 44.5)	-25.0(-57.4, 7.3)	-21.8(-48.7, 5.0)
Widowhood	-0.9(-12.8, 10.9)	-0.8 (-12.2, 10.6)	-8.4(-19.7, 3.0)	-7.7 (-18.8, 3.3)	11.2(-2.0, 24.5)	13.0(2.1, 24.0)
Wealth index †						
1st quarter (richest)	36.6(29.2, 44.1)	33.6(26.3, 40.9)	64.8(57.6, 72.0)	62.3(55.2, 69.4)	77.0(68.6, 85.3)	70.0(63.0, 77.0)
2nd quarter	-6.3(-17.3, 4.7)	-1.8(-12.6, 8.9)	-1.9(-12.5, 8.8)	2.0(-8.5, 12.5)	**-15.1(-27.5, -2.7)**	-4.1 (-14.5, 6.3)
3rd quarter	**-11.4(-21.8, -1.1)**	-7.2(-17.4, 2.9)	-2.4(-12.4, 7.7)	0.9(-9.0, 10.8)	-4.4(-16.0, 7.3)	5.0(-4.8, 14.9)
4th quarter (poorest)	**-11.9(-22.2, -1.5)**	-8.3(-18.4, 1.8)	-0.5(-10.6, 9.6)	2.3(-7.6, 12.2)	-11.0(-22.7, 0.7)	-3.0(-12.8, 6.8)
Trend	**-4.1(-7.4, -0.8)**	-3.0(-6.2, 0.2)	-0.2(-3.4, 3.0)	0.6(-2.5, 3.7)	-2.3(-6.0, 1.4)	0(-3.2, 3.1)

	DHP perceived health		DHP pain		DHP disability	
	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months	Adjusted*	Adjusted also for disability at 3 months
	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)	Mean(95% CI)
Type of stroke						
ICH	30.8(22.6, 39.0)	31.5(23.6, 39.4)	59.9(51.8, 67.9)	60.4(52.6, 68.2)	67.0(57.7, 76.4)	68.2 (60.4, 76.0)
IS	-2.3(-11.8, 7.1)	-3.2(-12.3, 5.9)	4.8(-4.4, 14.1)	4.2(-4.8, 13.2)	3.6(-7.1, 14.3)	2.1(-6.8, 11.1)
Severity of impairment						
NIHSS ≤ 7	33.9(29.1, 38.7)	30.2(25.3, 35.0)	68.5(63.9, 73.2)	65.0(60.3, 69.8)	76.4(70.9, 81.9)	66.8(62.1, 71.5)
NIHSS > 7	**-12.0(-19.5, -4.5)**	-2.8(-11.0, 5.3)	**-12.1(-19.5, -4.7)**	-3.4(-11.4, 4.6)	**-16.2(-24.9, -7.5)**	7.5(-0.5, 15.4)
Disability						
Least severe (mRS=0/1)	35.8(24.6, 47.0)	31.8(20.9, 42.7)	71.9(61.2, 82.6)	71.2(60.5, 82.0)	79.2(66.7, 91.7)	70.3(59.7, 80.8)
Intermediate (mRS=2/3)	-3.1(-15.1, 8.9)	0.5(-11.1, 12.2)	-9.6(-21.1, 1.9)	-8.9(-20.4, 2.7)	-8.7(-22.2, 4.7)	-0.5(-11.9, 10.8)
More severe (mRS=4/5)	-12.4(-26.2, 1.3)	-7.0(-20.4, 6.5)	-8.5(-21.7, 4.8)	-7.6(-20.9, 5.7)	-11.6(-27.1, 3.8)	0.5(-12.6, 13.6)
Trend	-6.9(-13.5, -0.2)	-4.3(-10.8, 2.2)	-3.1(-9.6, 3.3)	-2.8(-9.2, 3.7)	-5.2(-12.7, 2.3)	0.4(-5.9, 6.8)
Disability at 3 months						
Least severe (mRS=0/1)	43.8(37.2, 50.5)	n.n.	73.0(66.4, 79.6)	n.n.	94.8(88.3, 101.3)	n.n.
Intermediate (mRS=2/3)	**-22.7(-31.5, -13.9)**		-8.4(-17.1, 0.3)		**-16.6(-25.1, -8.0)**	
More severe (mRS=4/5)	**-22.5(-33.8, -11.3)**		**-22.2(-33.2, -11.1)**		**-67.6(-78.5, -56.7)**	
Trend	**-12.2(-17.8, -6.5)**		**-10.9(-16.4, -5.4)**		**-32.5(-38.1, -26.9)**	

* Adjusted for age, sex, proxy response and severity of impairment at admission

Chapter 8: Summary and Conclusions

8.1. Introduction

Stroke is the second most common cause of death [308], and a major contributor to morbidity and disability worldwide [308,309]. Up until the last decade or so, most of the data on the epidemiology of stroke had arisen from studies conducted in the developed world. There had been very little investigation of stroke in developing countries, likely due to a lack of resources and a shortage of adequately trained people to undertake the research. As outlined in Chapter 1, the evidence in respect of the burden of stroke in LMICs is limited with research largely confined to counts of events and acute outcomes, and with very limited examination of post-acute outcomes, particularly patient-centred ones such as HRQoL or costs. There is now some evidence [2] that the populations of LMICs are experiencing greater incidence of stroke than the populations of HICs. Recent reductions in communicable diseases in LMICs have resulted in greater longevity [64,65] and increased numbers of people surviving to the ages at which stroke is more common. It has been reported that rates of stroke among patients aged < 75 years in LMICs is more than three-fold those in HICs [2], translating to a greater burden at younger ages.

In response to this critical lack of information, this thesis has explored stroke in Viet Nam, a LMIC in south eastern Asia. This country shows the hallmarks of a country undergoing an 'epidemiological transition' with the percentage of the population aged ≥ 60 years (the ageing index in the context of a LMIC) having risen from 24.3% in 1999 to 35.5% in 2009 [66]. Concurrently, the cardiovascular risk factor profile of the population has worsened with reductions in physical activity and increases in intake of fat, salt and sugar [310] and in prevalence of smoking [311]. It is therefore likely that stroke, along with other chronic diseases, is becoming more common in Viet Nam.

The purpose of this thesis was to understand the current burden of stroke in Viet Nam. The approach was to look across different aspects of the burden of stroke including from the perspectives of the community, healthcare system and the patients. Investigation is made of the frequency of events, clinical manifestations, costs, case-fatality, functional outcomes and HRQoL. Unlike many studies of stroke in LMICs, this thesis explored the burden of stroke not only in acute phase, but also three months after discharge from hospital when functional status has somewhat stabilised [107,108,150,380].

The specific aims of this thesis were:

1. To determine the frequency of admissions over a 12 month period to a tertiary hospital including by stroke type and assess stroke severity and 28-day case-fatality, and to estimate the incidence of hospital-admitted first-ever stroke in Ho Chi Minh City;

2. To investigate case-fatality and functional outcomes three months after stroke;

3. To estimate the societal costs of stroke, including direct medical costs of treatment and the associated direct non-medical and indirect costs incurred during hospitalisation;

4. To assess the reliability and validity of assessments of health-related quality of life (HRQoL) from patient and proxy responses to the Duke Health Profile (DHP);

5. To assess the HRQoL of stroke survivors and to identify factors related to poor HRQoL three months post stroke.

8.2. Major findings and implications

Surveillance of stroke presentations over 12 months (Chapter 3)

Significance

It has been reported that the age-standardised incidence of stroke in LMICs is up to 23% greater than in HICs [2]. For the reasons outlined in the previous section, it is likely that stroke is becoming more common in Viet Nam, but there have been only two studies of stroke in the country [108,107] and one of those was conducted over 20 years ago [108]. This study is the first systematic surveillance of stroke admissions in Ho Chi Minh City, Viet Nam's largest city. It was conducted to determine the frequency of admission of different types of stroke, as well as the profile of stroke severity and 28 day case-fatality. A secondary aim was to attempt to estimate the incidence of hospital-admitted first-ever stroke across Ho Chi Minh City using population data and geospatial analysis.

Findings

The principal findings of this study were that among 5,017 (54.3% male, 75.6% first-ever stroke) patients with stroke, the mean age of stroke onset was 61.8 (SD 13.1) years for males and 67.5 (SD 13.2) years for females with more males (58.6%) than females (39.1%) aged <65 years at onset. Ischaemic stroke was the dominant type, and 77.5% of patients had moderate-to-severe disability (mRS=3/4/5) including 51.7% with severe disability (mRS=4/5) assessed on the modified Rankin Scale (mRS). Slurred speech, limb weakness and face weakness were the most common symptoms and signs of stroke. Age standardised to the new world standard population, the estimated incidence density of hospital-admitted stroke was 124.1 (95% confidence interval 99.7, 148.5) per 100,000 for males and 101.6 (95% confidence interval 74.8, 128.4) per 100,000 for females. The confirmed case-fatality at 28 days among patients with known vital status was 12.2% (males 11.8%, females 12.8%), with another 18% of patients having unknown vital status due to loss to follow-up.

Implications

The findings on stroke occurrence in respect of mean age at diagnosis and type of stroke are similar to those of studies conducted in other LMICs. The mean age of stroke onset was much lower than that found in HICs, however. This lower age of onset has potential implications for the ongoing economic development of Viet Nam. Although the country is rapidly becoming 'westernised', men are still largely responsible for providing the main income of Vietnamese families. Occurrence of stroke at young ages in the male population could lead to reductions in the labour workforce and economic hardship for the families of patients.

The proportion of cases with moderate-to-severe disability at admission was larger than that reported for other LMICs. This may be due, at least in part, to the data collection being from a tertiary referral hospital that receives more severe cases than smaller provincial hospitals. Verifying this would require stroke surveillance in provincial general hospitals and district hospitals. Further investigation of early management of stroke, with monitoring of the time

from the onset of stroke to the time of admission to a hospital, and of the management of major risk factors for stroke in the community (such as high blood pressure, atrial fibrillation and diabetes), would assist in determining why patients admitted to this hospital include greater proportions of those with more severe stroke than is usual in LMICs. Moreover, further research to understand the level of stroke care in hospitals that do not have specialised stroke treatment should be undertaken.

The similarity in clinical presentation of stroke patients in Viet Nam as elsewhere suggests that campaigns inform HICs, to raise awareness of the early signs and symptoms of stroke that would prompt an early hospital admission, can be considered for adoption in Viet Nam.

The incidence density and 28-day case-fatality were lower than expected. This is possibly due to under-ascertainment of mild cases at one end of the severity spectrum and of severe cases at the other. A factor contributing to under-ascertainment of severe cases is that Vietnamese cultural beliefs favour palliation at home, with the result that hospital-based studies may never completely ascertain all cases of stroke in this country. While there is no routine death registration and the lack of medically-certified cause-of-death data in Viet Nam remains, verbal autopsy can and has been used to provide reliable diagnoses of stroke and more complete ascertainments of death due to stroke in rural communities in Viet Nam [381]. There should be efforts made to investigate the practicability of implementing 'Step 2' and 'Step 3' of the WHO STEPS-Stroke methodology within Ho Chi Minh City in order to ascertain the population-wide incidence of stroke.

Case-fatality and functional status at three months after stroke onset (Chapter 4)

Significance

Observations about case-fatality and functional outcomes after stroke have come largely from studies conducted in HICs. Those studies show that reduced functional status or disability is common among survivors. It has been reported that approximately 30-40% of patients will have reduced function three months after stroke. Prior to this study, information about stroke patients after discharge from hospital was scarce in Viet Nam. This type of information is critical for planning the response to the growing burden of stroke in Viet Nam. Responding to this paucity of information, the author followed a cohort of first-ever stroke patients admitted to a stroke unit in a tertiary teaching hospital for three months after stroke and assessed case-fatality and functional outcomes at three months post stroke.

Findings

Among 450 consecutive patients recruited at baseline and followed with a low proportion (6.1%) of loss to follow-up, in-hospital case-fatality was 3.3%, 28-day case-fatality was 6.7%, and three-month case-fatality was 10.4% among patients with known vital status. One-third of patients had 'least severe disability' (mRS=0/1), one-third had 'intermediate disability' (mRS=2/3) and another one-third had 'most severe disability' (mRS=4/5). Over the three months following discharge, one-half of patients had improvements in their functional status, while one-quarter had worsened functional status. Men were found to have greater improvement in function than women.

Implications

As found in the surveillance study, and possibly for the same reasons, case-fatality was lower than that reported for other LMICs. The 28-day case-fatality in this study was much lower than that in a stroke registry study conducted at Da Nang Hospital, which is a provincial general hospital lacking a stroke unit and servicing a population in which the prevalence of untreated hypertension is high [107]. Furthermore, a national survey of risk factors for non-communicable disease conducted in provinces representative of the eight ecological areas of Viet Nam has provided evidence that the proportion of Ho Chi Minh City residents who are under treatment for high blood pressure is higher than that of other provinces. This suggests that better management of high blood pressure in the community, and providing more specialist stroke units in provincial hospitals, should be considered to prevent strokes and improve outcomes following stroke in Viet Nam.

The proportion of patients with severe functional limitations three months after stroke, and the proportion that had reductions in function over the three months, were similar to the findings of studies conducted in other LIMICs. However, it should be kept in mind that these outcomes were from a study conducted from a study of patients treated in one of the three major public hospitals with a specialist stroke unit, and with advanced imaging equipment and well-trained staff, in the largest city of Viet Nam. The proportion of patients with functional dependence following treatment for stroke in a provincial general hospital without a specialised stroke unit, or in a community hospital, would be higher.

Although the dependency of stroke survivors in Viet Nam is high, facilities required for support of people with such severe disability are not available. Even basic amenities such as sealed footpaths and public transport are lacking. There are no social support programs to identify the needs of patients in their homes and provide necessary home modifications. Stroke survivors, particularly those with more severe disability after stroke, are likely to be isolated in their homes and totally dependent on the care provided by their families. It is recommended that public health professionals and health policy makers should address the needs of this vulnerable group of people.

Costs of stroke in hospital (Chapter 5)

Significance

The economic burden of stroke including direct (medical and non-medical) and indirect (lost productivity or loss of income and caregiver burden) costs are likely to differ between countries due to differences in the presentation of stroke, its management and the costs assigned to resource use [326,327]. A limitation of existing work in this area is that most studies of the costs of stroke, particularly studies conducted in LMICs, have focused on direct costs without estimation of indirect costs. There has not been a previous report of the costs associated with the treatment of stroke in Viet Nam. This study provides the first estimates of the societal costs of stroke, including direct medical costs of treatment and the associated direct non-medical and indirect costs. Predictors of these costs of stroke during hospitalisation are identified.

Findings

From a societal perspective, the mean (SD) total costs per stroke admission were USD 963 (SD 968), comprising of USD 560 (SD 562) for direct medical costs, USD 171 (SD 486) for

direct non-medical costs, and USD 240 (SD 392) for indirect costs. The mean (SD) length of stay was 6.6 days (SD 4.2). Diagnostic imaging, medications and bed-day fees were the largest contributors to direct medical costs and overall costs were greater for patients with comorbidity. Health insurance reduced out-of-pocket direct medical costs by 56%. Severity of stroke, length of stay and household wealth were the major predictors of treatment cost of stroke.

Implications

Despite relatively short average length of stay and possibly under-estimated indirect costs, the total costs of treatment were two-to-three times the median monthly income of patients, suggesting that stroke incurs substantial costs for both society and the patients' families. Most stroke patients must rely on the support of relatives for payment of the hospital costs. Health insurance co-payments significantly reduce the out-of-pocket expenses for the families of insured patients. Viet Nam is moving towards universal healthcare with increased health insurance coverage of the population. This will help to reduce the burden of direct medical costs on patients.

The stroke unit in this hospital is one of the leading stroke units in public hospitals in Ho Chi Minh City, with a high standard of diagnostic imaging techniques and treatment in accordance with guidelines. The direct medical costs of stroke treatment as measured in this study would be broadly similar to treatment costs in other hospitals with stroke units, but higher than the treatment costs in general departments of provincial or community hospitals without a specialised stroke unit. With this caveat, our estimates of treatment costs of stroke should provide reliable, evidence-based guidance for public health practitioners and health policy-makers in Viet Nam.

It should borne in mind that the estimates of direct non-medical costs presented in this study were derived from information provided by a cohort of patients who were Ho Chi Minh City residents at the time of stroke onset. However, another 40% of stroke patients admitted to this stroke unit were residents of other provinces at some distance from Ho Chi Minh City. The direct non-medical costs for food, transportation and other sundry expenses for those patients and their caregivers would be higher. Furthermore, the estimates of indirect costs made in this study were based on loss of income and took no account of loss of productivity not reflected by loss of income, and no allowance was made for loss of leisure time. If these other sources of loss were taken into account, the estimated burden of indirect costs for patients and their family would be much greater.

Reliability and validity of health-related quality of life instruments (Chapter 6)

Significance

Because a major objective of this thesis was to explore patient-centred outcomes by measuring HRQoL, there was a requirement to select a dependable instrument with which to measure this construct. Review of the literature and discussions with local colleagues confirmed that there were no instruments available for which the validity of measurements of the HRQoL of stroke patients in Viet Nam, or anywhere else for that matter, had been assessed. One instrument – the Duke Health Profile (DHP) – had been translated and culturally adapted for use in the adolescent and general adult populations of Ho Chi Minh City, Viet Nam. This generic instrument provides assessments of dimensions of HRQoL that

are not captured by other HRQoL instruments such as the EuroQol EQ-5D. These other dimensions are social and mental health, which are potentially important after stroke. Therefore, the aim of this study was to assess the reliability and validity of measurements of HRQoL for stroke patients in Viet Nam made with the DHP, including when completed by a proxy on behalf of the patient.

Findings

Overall, the DHP was found to have moderate reliability when completed by patients or when completed by a proxy on behalf of the patient. For example, the intra-class correlations (ICCs) ranged from 0.60 to 0.86 for patient test-retest and from 0.55 to 0.98 for patient-proxy agreement. The ICCs were greatest for physical functioning components (patient test-retest 0.63–0.86, patient-proxy: 0.69–0.98). The mean differences between test and retest assessments of HRQoL by patients were small and not clinically meaningful, and were not consistently associated with sex, age, type of stroke, or severity of impairment or disability. Direct assessments by the patient were on average greater than those obtained from the proxy. The correlations between the DHP dimensions and EQ-5D components were generally stronger when they measured similar constructs (r=0.53–0.66), and were lower for less related constructs (r=0.11–0.43).

Implications

The DHP may be used to measure the HRQoL of stroke patients, and possibly of people with other chronic diseases, and of patients with severe health conditions who cannot response directly to the DHP and require caregivers to provide information on their behalf.

Health-related to quality of life of stroke survivors three months after stroke (Chapter 7)

Significance

To fully understand the burden of stroke in LMICs such as Viet Nam, the HRQoL of stroke survivors should be assessed. This is because HRQoL is an important patient-centred outcome. To date, there has not been a study of HRQoL of stroke survivors in Viet Nam. To correct this deficiency, a study providing assessment of HRQoL of stroke survivors was conducted. The aims were to assess the HRQoL of survivors three months following a first-ever stroke in Viet Nam, and to identify factors related to poor HRQoL.

Findings

The mean DHP general health score was 58.7 (SD 17.8). The mean EQ-5D utility score was 0.67 (SD 0.33) and the mean VAS score was 61.3 (SD 20.4). For those with the least severity of disability (mRS=0/1) at admission, the mean DHP overall score was 66.9 (SD 14.7) and similar to that of a general population sample of Ho Chi Minh City [62.7(SD 18.2)]. The mean DHP overall score of patients with intermediate severity (mRS=2/3) and of those with most severe disability (mRS=4/5) at admission were 5.2 and 12.9 points lower respectively. The study factors associated with poorer HRQoL were increasing age, female sex, greater severity stroke at admission and greater severity of disability at three months. Only female sex and severity of disability at three months were independently associated with poorer HRQoL.

Implications

Suggesting that severe strokes reduce well-being, measurements of HRQoL made with the DHP were substantially lower on average for patients with most severe disability (mRS=4/5) than the mean value for the general population from which they were drawn. For patients with less severe disability, their HRQoL was similar on average to that of members of the general population.

Self-reported HRQoL was lower for female patients than for male patients, with the greatest deficits in the physical health, pain and depression dimensions. The study of functional outcomes at three months (Chapter 4) produced key findings that female patients had relatively greater severity of disability at three month than male patients and fewer had recovered during the intervening period, but the female deficits in general health and depression, and greater awareness of pain, remained after adjustment for severity of disability. A contributing factor may be the central role that the older woman plays in family life in Viet Nam. A disabling stroke would leave her unable to perform that role, and reverse family dependence relationships with a possible detriment to her social and mental health.

It was important to confirm that the factors associated with poorer outcomes including HRQoL are similar to those found in other populations, suggesting application in Viet Nam of strategies for management of stroke primarily to reduce stroke severity and improve recovery that have been developed in HICs and are known to be effective.

In Viet Nam, caregivers play an important role in caring for patients following a stroke, including by providing care in hospital and later at home. They typically have a close relationship with patients, being their spouse, parent or offspring in most cases. After being discharged from the hospital, the majority of participants in this study needed to receive care and around 40% were dependent on that care for activities of daily living (mRS $\geq$ 3). In the absence of residential aged care facilities such as nursing homes and rehabilitation centres, and without social support programs being available for patients following stroke, a substantial burden of care falls on caregivers in Viet Nam.

8.3. Recommendations for future research

The research reported in this thesis has provided important findings in relation to the occurrence, clinical presentation and treatment costs of stroke in Viet Nam and on outcomes three months following stroke in Viet Nam.

It has also brought to light some gaps in information that need to be addressed in future research. These gaps are listed below:

1. The extent of under-ascertainment of mild cases at one end of the severity spectrum, and particularly of severe cases at the other end of the spectrum, is unknown. Under-ascertainment is to be expected in a hospital-based study, and well-designed community-based studies are needed to provide a more complete account of stroke occurrence and of the overall burden of stroke in Viet Nam. The success of the hospital-based surveillance at 115 People's Hospital is a first step towards comprehensive stroke surveillance in Viet Nam;

2. This study has not provided information on stroke patients treated in a provincial general hospital or a community hospital without a stroke unit. Further studies

investigating stroke care across a range of hospital are required to complete the description of the clinical pathways and outcomes for stroke patients in Viet Nam. Ultimately, quality standards for the hospitals management of acute stroke should be developed in Viet Nam;

3. The contribution of delayed hospital admission to poor outcomes after stroke has not yet been investigated in Viet Nam. There is no centrally managed ambulance service in Viet Nam. In addition, the precursors of delayed admission – such as lack of awareness of stroke signs and symptoms by patients and caregivers, slow initial reaction to stroke and ineffective treatment-seeking behaviours at the time of onset – should be investigated;

4. The information collected on costs of treatment for stroke included neither the losses of productivity not reflected by loss of income nor the larger indirect costs incurred by patients who travel great distances to receive treatment. More information on the costs of stroke during and after hospitalisation for an acute intensive treatment should be collected to describe more fully the burden of cost on patients and their families. It is also important to examine the extent of hardship on patients' families following a stroke, including assessment of whether total health expenditure is so high as to be deemed catastrophic for a family;

5. The longer-term outcomes of stroke survivors in Viet Nam have not been investigated. The success of the three-month follow-up of this cohort suggests that it should be feasible to follow a cohort of stroke patients for longer periods of time to investigate case-fatality, disability and HRQoL of stroke survivors after one or more years;

6. Assessment of HRQoL of stroke survivors with stroke-specific instruments has not been attempted in Viet Nam. In this study, measurements were made using two generic instruments (the DHP and EQ-5D). A stroke-specific instrument – such as the Stroke Specific Quality of Life Scale or the Stroke and Aphasia Quality of Life Scale – should be translated, culturally adapted and used to assess HRQoL of stroke survivors in Viet Nam;

7. There is a lack of information on population norms for the instruments that can be used to measure HRQoL of Vietnamese people. These data would be important for comparisons of outcomes across a range of conditions, and also for use in evaluation of programs to prevent and manage those conditions;

8. This study has provided the first information on the impact on Vietnamese caregivers of caring for a person with stroke, but the picture is far from complete. The burden of stroke on caregivers seems to be substantial in Viet Nam. Further studies should be conducted to explore the level of physical function and health-related quality of life of caregivers of stroke patients, and of patients with other conditions. The specific influence of caregiver characteristics and well-being on patient outcomes should be investigated.

8.4. Conclusion

The thesis provides original findings in respect of the epidemiology of stroke in urban Viet Nam and the burden of stroke on patients, their families, the healthcare system and society. A particularly novel aspect was the assessment of the outcomes at three months after stroke onset. Stroke in Viet Nam occurs at lesser mean age of onset and with three-quarters of patients having moderate-to-severe disability at admission. Three months following stroke, one-third of patients still had significant levels of disability and substantially lower psychological well-being. Stroke also imposes a huge cost on society and on the patient's families. The true burden may be much larger, because the information analysed in this study was collected from patients who were treated at a major teaching public hospital with a stroke unit in the largest city of Viet Nam. Effective plans to diminish the burden of stroke in Viet Nam are required.

Bibliography

1. Tran, P. L., Leigh Blizzard, C., Srikanth, V., Hanh, V. T., Lien, N. T., Thang, N. H., et al. (2015). Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Vietnam. *Qual Life Res*

2. Feigin, V. L., Forouzanfar, M. H., Krishnamurthi, R., Mensah, G. A., Connor, M., Bennett, D. A., et al. (2014). Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet, 383*(9913), 245-54

3. Hatano, S. (1976). Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organisation, 54*(5), 541-53

4. World Health Organization (2006). WHO STEPS Stroke Manual: The WHO STEPwise approach to stroke surveillance. http://www.who.int/chp/steps/Manual.pdf.

5. Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J., Culebras, A., et al. (2013). An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 44*(7), 2064-89

6. Ribo, M., & Grotta, J. C. (2006). Latest advances in intracerebral hemorrhage. *Curr Neurol Neurosci Rep, 6*(1), 17-22

7. Bamford, J., Sandercock, P., Dennis, M., Burn, J., & Warlow, C. (1991). Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet, 337*(8756), 1521-6

8. Asdaghi, N., Jeerakathil, T., Hameed, B., Saini, M., McCombe, J. A., Shuaib, A., et al. (2011). Oxfordshire community stroke project classification poorly differentiates small cortical and subcortical infarcts. *Stroke, 42*(8), 2143-8

9. Bamford, J. M. (2000). The role of the clinical examination in the subclassification of stroke. *Cerebrovasc Dis, 10 Suppl 4*, 2-4

10. Adams, H. P., Jr., Bendixen, B. H., Kappelle, L. J., Biller, J., Love, B. B., Gordon, D. L., et al. (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke, 24*(1), 35-41

11. Desalu, O. O., Wahab, K. W., Fawale, B., Olarenwaju, T. O., Busari, O. A., Adekoya, A. O., et al. (2011). A review of stroke admissions at a tertiary hospital in rural Southwestern Nigeria. *Ann Afr Med, 10*(2), 80-5

12. Dalal, P. M., Bhattacharjee, M., Vairale, J., & Bhat, P. (2008). Mumbai stroke registry (2005-2006)-surveillance using WHO steps stroke instrument-challenges and opportunities. *J Assoc Physicians India, 56*, 675-80

13. Krishnamurthi, R. V., Feigin, V. L., Forouzanfar, M. H., Mensah, G. A., Connor, M., Bennett, D. A., et al. (2013). Global and regional burden of first-ever ischaemic and

haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health, 1*(5), e259-81

14. Banerjee, T. K., Mukherjee, C. S., & Sarkhel, A. (2001). Stroke in the urban population of Calcutta--an epidemiological study. *Neuroepidemiology, 20*(3), 201-7

15. Liu, M., Wu, B., Wang, W. Z., Lee, L. M., Zhang, S. H., & Kong, L. Z. (2007). Stroke in China: epidemiology, prevention, and management strategies. *Lancet Neurol, 6*(5), 456-64

16. Feigin, V. L., Lawes, C. M., Bennett, D. A., Barker-Collo, S. L., & Parag, V. (2009). Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol, 8*(4), 355-69

17. Das, S. K., Banerjee, T. K., Biswas, A., Roy, T., Raut, D. K., Mukherjee, C. S., et al. (2007). A prospective community-based study of stroke in Kolkata, India. *Stroke, 38*(3), 906-10

18. Kumral, E., Ozkaya, B., Sagduyu, A., Sirin, H., Vardarli, E., & Pehlivan, M. (1998). The Ege Stroke Registry: a hospital-based study in the Aegean region, Izmir, Turkey. Analysis of 2,000 stroke patients. *Cerebrovasc Dis, 8*(5), 278-88

19. Arjundas, D., Pandiyan, U., Arjundas, G., & Henry, B. (2007). *Surveillance of stroke: WHO STEP-wise approach: A Chennai stroke unit report* (Vol. 10, Vol. 3).

20. de Carvalho, J. J., Alves, M. B., Viana, G. A., Machado, C. B., dos Santos, B. F., Kanamura, A. H., et al. (2011). Stroke epidemiology, patterns of management, and outcomes in Fortaleza, Brazil: a hospital-based multicenter prospective study. *Stroke, 42*(12), 3341-6

21. Minelli, C., Fen, L. F., & Minelli, D. P. (2007). Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matao, Brazil: a population-based prospective study. *Stroke, 38*(11), 2906-11

22. Feigin, V. L. (2007). Stroke in developing countries: can the epidemic be stopped and outcomes improved? *The Lancet Neurology, 6*(2), 94-97

23. Goldstein, L. B., Jones, M. R., Matchar, D. B., Edwards, L. J., Hoff, J., Chilukuri, V., et al. (2001). Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. *Stroke, 32*(5), 1091-8

24. Appelros, P., Stegmayr, B., & Terent, A. (2009). Sex differences in stroke epidemiology: a systematic review. *Stroke, 40*(4), 1082-90

25. Reeves, M. J., Bushnell, C. D., Howard, G., Gargano, J. W., Duncan, P. W., Lynch, G., et al. (2008). Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol, 7*(10), 915-26

26. Nagaraja, D., Gururaj, G., Girish, N., Panda, S., Roy, A. K., Sarma, G. R., et al. (2009). Feasibility study of stroke surveillance: data from Bangalore, India. *Indian J Med Res, 130*(4), 396-403

27. Truelsen, T., Heuschmann, P. U., Bonita, R., Arjundas, G., Dalal, P., Damasceno, A., et al. (2007). Standard method for developing stroke registers in low-income and middle-income

countries: experiences from a feasibility study of a stepwise approach to stroke surveillance (STEPS Stroke). *Lancet Neurol, 6*(2), 134-9

28. Sridharan, S. E., Unnikrishnan, J. P., Sukumaran, S., Sylaja, P. N., Nayak, S. D., Sarma, P. S., et al. (2009). Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. *Stroke, 40*(4), 1212-8

29. Misbach, J., & Ali, W. (2001). Stroke in Indonesia: a first large prospective hospital-based study of acute stroke in 28 hospitals in Indonesia. *J Clin Neurosci, 8*(3), 245-9

30. Goulart, A. C., Bustos, I. R., Abe, I. M., Pereira, A. C., Fedeli, L. M., Bensenor, I. M., et al. (2010). A stepwise approach to stroke surveillance in Brazil: the EMMA (Estudo de Mortalidade e Morbidade do Acidente Vascular Cerebral) study. *Int J Stroke, 5*(4), 284-9

31. General Statistics Office (2011). Education in Vietnam: An analysis of key indicators. *Vietnam Population and Housing Census 2009*. Ha Noi: General Statistics Office.

32. Correia, M., Silva, M. R., Matos, I., Magalhaes, R., Lopes, J. C., Ferro, J. M., et al. (2004). Prospective community-based study of stroke in Northern Portugal: incidence and case fatality in rural and urban populations. *Stroke, 35*(9), 2048-53

33. Sudlow, C. L., & Warlow, C. P. (1997). Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. *Stroke, 28*(3), 491-9

34. Homer, D., Whisnant, J. P., & Schoenberg, B. S. (1987). Trends in the incidence rates of stroke in Rochester, Minnesota, since 1935. *Ann Neurol, 22*(2), 245-51

35. Stewart, J. A., Dundas, R., Howard, R. S., Rudd, A. G., & Wolfe, C. D. (1999). Ethnic differences in incidence of stroke: prospective study with stroke register. *BMJ,, 318*(7189), 967-71

36. Syme, P. D., Byrne, A. W., Chen, R., Devenny, R., & Forbes, J. F. (2005). Community-based stroke incidence in a Scottish population: the Scottish Borders Stroke Study. *Stroke, 36*(9), 1837-43

37. Appelros, P., Nydevik, I., Seiger, A., & Terent, A. (2002). High incidence rates of stroke in Orebro, Sweden: Further support for regional incidence differences within Scandinavia. *Cerebrovasc Dis, 14*(3-4), 161-8

38. Smadja, D., Cabre, P., May, F., Fanon, J. L., Rene-Corail, P., Riocreux, C., et al. (2001). ERMANCIA: Epidemiology of Stroke in Martinique, French West Indies: Part I: methodology, incidence, and 30-day case fatality rate. *Stroke, 32*(12), 2741-7

39. O'Donnell, M. J., Xavier, D., Liu, L., Zhang, H., Chin, S. L., Rao-Melacini, P., et al. (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet, 376*(9735), 112-23

40. Allen, C. L., & Bayraktutan, U. (2008). Risk factors for ischaemic stroke. *Int J Stroke, 3*(2), 105-16

41. Qureshi, A. I., Suri, M. F., Yahia, A. M., Suarez, J. I., Guterman, L. R., Hopkins, L. N., et al. (2001). Risk factors for subarachnoid hemorrhage. *Neurosurgery, 49*(3), 607-12; discussion 12-3

42. Juvela, S., Hillbom, M., & Palomaki, H. (1995). Risk factors for spontaneous intracerebral hemorrhage. *Stroke, 26*(9), 1558-64

43. Shah, R. S., & Cole, J. W. (2010). Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther, 8*(7), 917-32

44. Bonita, R., Duncan, J., Truelsen, T., Jackson, R. T., & Beaglehole, R. (1999). Passive smoking as well as active smoking increases the risk of acute stroke. *Tob Control, 8*(2), 156-60

45. Wolf, P. A., D'Agostino, R. B., Kannel, W. B., Bonita, R., & Belanger, A. J. (1988). Cigarette smoking as a risk factor for stroke. The Framingham Study. *Jama, 259*(7), 1025-9

46. Peters, S. A., Huxley, R. R., & Woodward, M. (2013). Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke, 44*(9), 2394-401

47. Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., Shah, A. D., Denaxas, S., et al. (2014). Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet, 383*(9932), 1899-911

48. Feigin, V. L., Rinkel, G. J., Lawes, C. M., Algra, A., Bennett, D. A., van Gijn, J., et al. (2005). Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke, 36*(12), 2773-80

49. Bonita, R. (1986). Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. *Stroke, 17*(5), 831-5

50. Longstreth, W. T., Jr., Nelson, L. M., Koepsell, T. D., & van Belle, G. (1992). Cigarette smoking, alcohol use, and subarachnoid hemorrhage. *Stroke, 23*(9), 1242-9

51. Paul, S. L., Thrift, A. G., & Donnan, G. A. (2004). Smoking as a crucial independent determinant of stroke. *Tob Induc Dis, 2*(2), 67-80

52. Teunissen, L. L., Rinkel, G. J., Algra, A., & van Gijn, J. (1996). Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke, 27*(3), 544-9

53. Thrift, A. G., Srikanth, V., & Evans, R. G. (2010). How generalisable is INTERSTROKE? *Lancet, 376*(9752), 1538-9; author reply 39

54. Kaul, S., Bandaru, V. C., Suvarna, A., & Boddu, D. B. (2009). Stroke burden and risk factors in developing countries with special reference to India. *J Indian Med Assoc, 107*(6), 358, 67-70

55. Walker, R. W., Jusabani, A., Aris, E., Gray, W. K., Unwin, N., Swai, M., et al. (2013). Stroke risk factors in an incident population in urban and rural Tanzania: a prospective, community-based, case-control study. *The Lancet Global Health, 1*(5), e282-e88

56. Copstein, L., Fernandes, J. G., & Bastos, G. A. (2013). Prevalence and risk factors for stroke in a population of Southern Brazil. *Arq Neuropsiquiatr, 71*(5), 294-300

57. Zuhaid, M., Salman, Chawla, J. A., Farooq, U., Ahmad, A., Khan, S., et al. (2014). Frequency of modifiable risk factors in stroke patients. *J Ayub Med Coll Abbottabad, 26*(2), 235-8

58. Brainin, M., Teuschl, Y., & Kalra, L. (2007). Acute treatment and long-term management of stroke in developing countries. *Lancet Neurol, 6*(6), 553-61

59. Hanchaiphiboolkul, S., Poungvarin, N., Nidhinandana, S., Suwanwela, N. C., Puthkhao, P., Towanabut, S., et al. (2011). Prevalence of stroke and stroke risk factors in Thailand: Thai Epidemiologic Stroke (TES) Study. *J Med Assoc Thai, 94*(4), 427-36

60. Garbusinski, J. M., van der Sande, M. A., Bartholome, E. J., Dramaix, M., Gaye, A., Coleman, R., et al. (2005). Stroke presentation and outcome in developing countries: a prospective study in the Gambia. *Stroke, 36*(7), 1388-93

61. Feigin, V. L., & Krishnamurthi, R. (2011). Stroke prevention in the developing world. *Stroke, 42*(12), 3655-8

62. Thorogood, M., Connor, M. D., Lewando-Hundt, G., Tollman, S., Ngoma, B., & Team, S. P. (2004). Secondary prevention of stroke--results from the Southern Africa Stroke Prevention Initiative (SASPI) study. *Bulletin of the World Health Organization, 82*(7), 503-08

63. Wasay, M., Khatri, I. A., & Kaul, S. (2014). Stroke in South Asian countries. *Nat Rev Neurol, 10*(3), 135-43

64. Donnan, G. A., Fisher, M., Macleod, M., & Davis, S. M. (2008). Stroke. *Lancet, 371*(9624), 1612-23

65. Paul, S. L., Srikanth, V. K., & Thrift, A. G. (2007). The large and growing burden of stroke. *Curr Drug Targets, 8*(7), 786-93

66. Ha Do, T. P., Feskens, E. J., Deurenberg, P., Mai, L. B., Khan, N. C., & Kok, F. J. (2011). Nationwide shifts in the double burden of overweight and underweight in Vietnamese adults in 2000 and 2005: two national nutrition surveys. *BMC Public Health, 11*, 62

67. Chen, X., Zhou, L., Zhang, Y., Yi, D., Liu, L., Rao, W., et al. (2014). Risk Factors of Stroke in Western and Asian Countries: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *BMC Public Health, 14*(1), 776

68. Ezzati, M., Hoorn, S. V., Lopez, A. D., Danaei, G., Rodgers, A., Mathers, C. D., et al. (2006). Comparative Quantification of Mortality and Burden of Disease Attributable to Selected Risk Factors. In A. D. Lopez, C. D. Mathers, M. Ezzati, D. T. Jamison, & C. J. L. Murray (Eds.), *Global Burden of Disease and Risk Factors* (Vol. 2, pp. 241-396). Washington (DC): World Bank The International Bank for Reconstruction and Development/The World Bank Group.

69. Lavados, P. M., Hennis, A. J., Fernandes, J. G., Medina, M. T., Legetic, B., Hoppe, A., et al. (2007). Stroke epidemiology, prevention, and management strategies at a regional level: Latin America and the Caribbean. *Lancet Neurol, 6*(4), 362-72

70. Eastern Stroke Coronary Heart Disease Collaborative Research. (1998). Blood pressure, cholesterol, and stroke in eastern Asia. *The Lancet, 352*(9143), 1801-07

71. MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., et al. (1990). Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet, 335*(8692), 765-74

72. Lloyd-Sherlock, P. (2010). Stroke in Developing Countries: Epidemiology, Impact and Policy Implications. *Development Policy Review, 28*(6), 693-709

73. Bui, T., Blizzard, C. L., Luong, N. K., Truong , L. V. N., Tran, Q. B., Ha, T. S., et al. (2014). Decling prevalence of tobacco smoking in Vietnam. *Nicotine Tob Res*

74. Bornstein, N. M. (2009). *Stroke: practical guide for clinicians*: Karger Medical and Scientific Publishers.

75. Rathore, S. S., Hinn, A. R., Cooper, L. S., Tyroler, H. A., & Rosamond, W. D. (2002). Characterization of incident stroke signs and symptoms: findings from the atherosclerosis risk in communities study. *Stroke, 33*(11), 2718-21

76. Ustrell-Roig, X., & Serena-Leal, J. (2007). [Stroke. Diagnosis and therapeutic management of cerebrovascular disease]. *Rev Esp Cardiol, 60*(7), 753-69

77. American Heart Association (2014). Spot a stroke: Stroke warning signs and symptoms. http://strokeassociation.org/STROKEORG/WarningSigns/Stroke-Warning-Signs-and-Symptoms_UCM_308528_SubHomePage.jsp. Accessed February 10, 2014.

78. Hennerici, M. G., Binder, J., & Szabo, K. (2012). Management of acute stroke. *Stroke*. Oxford: Oxford University Press.

79. Jauch, E. C., Saver, J. L., Adams, H. P., Jr., Bruno, A., Connors, J. J., Demaerschalk, B. M., et al. (2013). Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 44*(3), 870-947

80. Kernan, W. N., Ovbiagele, B., Black, H. R., Bravata, D. M., Chimowitz, M. I., Ezekowitz, M. D., et al. (2014). Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45*(7), 2160-236

81. Wahlgren, N., Ahmed, N., Dávalos, A., Ford, G. A., Grond, M., Hacke, W., et al. (2007). Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *The Lancet, 369*(9558), 275-82

82. Wardlaw, J. M., Zoppo, G., Yamaguchi, T., & Berge, E. (2003). Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*(3), Cd000213

83. Wardlaw, J. M., Murray, V., Berge, E., & Del Zoppo, G. J. (2009). Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*(4), Cd000213

84. Saver, J. L., Smith, E. E., Fonarow, G. C., Reeves, M. J., Zhao, X., Olson, D. M., et al. (2010). The "golden hour" and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset. *Stroke, 41*(7), 1431-9

85. Mazighi, M., Meseguer, E., Labreuche, J., & Amarenco, P. (2012). Bridging therapy in acute ischemic stroke: a systematic review and meta-analysis. *Stroke, 43*(5), 1302-8

86. Mayer, S. A., & Rincon, F. Treatment of intracerebral haemorrhage. *The Lancet Neurology, 4*(10), 662-72

87. Sahni, R., & Weinberger, J. (2007). Management of intracerebral hemorrhage. *Vasc Health Risk Manag, 3*(5), 701-9

88. Anderson, C. S., Huang, Y., Wang, J. G., Arima, H., Neal, B., Peng, B., et al. (2008). Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol, 7*(5), 391-9

89. Patarroyo, S. X., & Anderson, C. (2012). Blood pressure lowering in acute phase of stroke: latest evidence and clinical implications. *Ther Adv Chronic Dis, 3*(4), 163-71

90. Bederson, J. B., Connolly, E. S., Jr., Batjer, H. H., Dacey, R. G., Dion, J. E., Diringer, M. N., et al. (2009). Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke, 40*(3), 994-1025

91. Connolly, E. S., Jr., Rabinstein, A. A., Carhuapoma, J. R., Derdeyn, C. P., Dion, J., Higashida, R. T., et al. (2012). Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke, 43*(6), 1711-37

92. Murray, C. J., & Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet, 349*(9064), 1498-504

93. Malmgren, R., Warlow, C., Bamford, J., & Sandercock, P. (1987). Geographical and secular trends in stroke incidence. *Lancet, 2*(8569), 1196-200

94. Sudlow, C. L., & Warlow, C. P. (1996). Comparing stroke incidence worldwide: what makes studies comparable? *Stroke, 27*(3), 550-8

95. Coull, A. J., Silver, L. E., Bull, L. M., Giles, M. F., & Rothwell, P. M. (2004). Direct assessment of completeness of ascertainment in a stroke incidence study. *Stroke, 35*(9), 2041-5

96. Bonita, R., Broad, J. B., Anderson, N. E., & Beaglehole, R. (1995). Approaches to the problems of measuring the incidence of stroke: the Auckland Stroke Study, 1991-1992. *Int J Epidemiol, 24*(3), 535-42

97. Truelsen, T., Bonita, R., & Jamrozik, K. (2001). Surveillance of stroke: a global perspective. *Int J Epidemiol, 30 Suppl 1*, S11-6

98. World Health Organization (2006). *WHO STEPS Stroke Manual: The WHO STEPwise approach to stroke surveillance*. Geneva, World Health Organization.

99. Aho, K., Harmsen, P., Hatano, S., Marquardsen, J., Smirnov, V. E., & Strasser, T. (1980). Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ, 58*(1), 113-30

100. Mihalka, L., Smolanka, V., Bulecza, B., Mulesa, S., & Bereczki, D. (2001). A population study of stroke in West Ukraine: incidence, stroke services, and 30-day case fatality. *Stroke, 32*(10), 2227-31

101. Tsiskaridze, A., Djibuti, M., van Melle, G., Lomidze, G., Apridonidze, S., Gauarashvili, I., et al. (2004). Stroke incidence and 30-day case-fatality in a suburb of Tbilisi: results of the first prospective population-based study in Georgia. *Stroke, 35*(11), 2523-8

102. Powles, J., Kirov, P., Feschieva, N., Stanoev, M., & Atanasova, V. (2002). Stroke in urban and rural populations in north-east Bulgaria: incidence and case fatality findings from a 'hot pursuit' study. *BMC Public Health, 2*, 24

103. Walker, R. W., McLarty, D. G., Kitange, H. M., Whiting, D., Masuki, G., Mtasiwa, D. M., et al. (2000). Stroke mortality in urban and rural Tanzania. Adult Morbidity and Mortality Project. *Lancet, 355*(9216), 1684-7

104. Sajjad, A., Chowdhury, R., Felix, J. F., Ikram, M. A., Mendis, S., Tiemeier, H., et al. (2013). A systematic evaluation of stroke surveillance studies in low- and middle-income countries. *Neurology, 80*(7), 677-84

105. Anderson, C. S., Jamrozik, K. D., Burvill, P. W., Chakera, T. M., Johnson, G. A., & Stewart-Wynne, E. G. (1993). Ascertaining the true incidence of stroke: experience from the Perth Community Stroke Study, 1989-1990. *Med J Aust, 158*(2), 80-4

106. Thrift, A. G., Dewey, H. M., Macdonell, R. A., McNeil, J. J., & Donnan, G. A. (2000). Stroke incidence on the east coast of Australia: the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke, 31*(9), 2087-92

107. Tirschwell, D. L., Ton, T. G., Ly, K. A., Van Ngo, Q., Vo, T. T., Pham, C. H., et al. (2012). A prospective cohort study of stroke characteristics, care, and mortality in a hospital stroke registry in Vietnam. *BMC Neurol, 12*, 150

108. Le, V. T., Le, T. L., Nguyen, T. H., Nguyen, H. H., Dao, T. X., Nguyen, V. T., et al. (1999). Les accidents vasculaires cerebraux au Sud Viet-nam: etude epidemiologique. *Rev Neurol (Paris), 155*(2), 137-40

109. Thrift, A. G., Cadilhac, D. A., Thayabaranathan, T., Howard, G., Howard, V. J., Rothwell, P. M., et al. (2014). Global stroke statistics. *Int J Stroke, 9*(1), 6-18

110. Kolominsky-Rabas, P. L., Sarti, C., Heuschmann, P. U., Graf, C., Siemonsen, S., Neundoerfer, B., et al. (1998). A prospective community-based study of stroke in Germany--the Erlangen Stroke Project (ESPro): incidence and case fatality at 1, 3, and 12 months. *Stroke, 29*(12), 2501-6

111. Ellekjaer, H., Holmen, J., Indredavik, B., & Terent, A. (1997). Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate. *Stroke, 28*(11), 2180-4

112. Hamad, A., Hamad, A., Sokrab, T. E., Momeni, S., Mesraoua, B., & Lingren, A. (2001). Stroke in Qatar: a one-year, hospital-based study. *J Stroke Cerebrovasc Dis, 10*(5), 236-41

113. Oveisgharan, S., Sarrafzadegan, N., Shirani, S., Hosseini, S., Hasanzadeh, P., & Khosravi, A. (2007). Stroke in Isfahan, Iran: hospital admission and 28-day case fatality rate. *Cerebrovasc Dis, 24*(6), 495-9

114. Jaya, F., Win, M. N., Abdullah, M. R., Abdullah, M. R., & Abdullah, J. M. (2002). Stroke patterns in Northeast Malaysia: a hospital-based prospective study. *Neuroepidemiology, 21*(1), 28-35

115. Brott, T., Adams, H. P., Jr., Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., et al. (1989). Measurements of acute cerebral infarction: a clinical examination scale. *Stroke, 20*(7), 864-70

116. D'Olhaberriague, L., Litvan, I., Mitsias, P., & Mansbach, H. H. (1996). A reappraisal of reliability and validity studies in stroke. *Stroke, 27*(12), 2331-6

117. De Haan, R., Horn, J., Limburg, M., Van Der Meulen, J., & Bossuyt, P. (1993). A comparison of five stroke scales with measures of disability, handicap, and quality of life. *Stroke, 24*(8), 1178-81

118. Goldstein, L. B., Bertels, C., & Davis, J. N. (1989). Interrater reliability of the NIH stroke scale. *Arch Neurol, 46*(6), 660-2

119. Goldstein, L. B., & Samsa, G. P. (1997). Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. *Stroke, 28*(2), 307-10

120. Lyden, P., Raman, R., Liu, L., Emr, M., Warren, M., & Marler, J. (2009). National Institutes of Health Stroke Scale certification is reliable across multiple venues. *Stroke, 40*(7), 2507-11

121. Rankin, J. (1957). Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J, 2*(5), 200-15

122. UK-TIA Study Group (1988). United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. UK-TIA Study Group. *Br Med J (Clin Res Ed), 296*(6618), 316-20

123. van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. J., & van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke, 19*(5), 604-7

124. Pinto, A. N., Melo, T. P., Lourenco, M. E., Leandro, M. J., Brazio, A., Carvalho, L., et al. (1998). Can a clinical classification of stroke predict complications and treatments during hospitalization? *Cerebrovasc Dis, 8*(4), 204-9

125. Wolfe, C. D., Taub, N. A., Woodrow, E. J., & Burney, P. G. (1991). Assessment of scales of disability and handicap for stroke patients. *Stroke, 22*(10), 1242-4

126. Salgado, A. V., Ferro, J. M., & Gouveia-Oliveira, A. (1996). Long-term prognosis of first-ever lacunar strokes. A hospital-based study. *Stroke, 27*(4), 661-6

127. Di Carlo, A., Lamassa, M., Pracucci, G., Basile, A. M., Trefoloni, G., Vanni, P., et al. (1999). Stroke in the very old : clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. *Stroke, 30*(11), 2313-9

128. Paciaroni, M., Arnold, P., Van Melle, G., & Bogousslavsky, J. (2000). Severe disability at hospital discharge in ischemic stroke survivors. *Eur Neurol, 43*(1), 30-4

129. Hacke, W., Kaste, M., Fieschi, C., Toni, D., Lesaffre, E., von Kummer, R., et al. (1995). Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *Jama, 274*(13), 1017-25

130. Kwiatkowski, T. G., Libman, R. B., Frankel, M., Tilley, B. C., Morgenstern, L. B., Lu, M., et al. (1999). Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med, 340*(23), 1781-7

131. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995). Tissue plasminogen activator for acute ischemic stroke *N Engl J Med, 333*(24), 1581-7

132. The Multicenter Acute Stroke Trial--Europe Study Group (1996). Thrombolytic therapy with streptokinase in acute ischemic stroke *N Engl J Med, 335*(3), 145-50

133. Barnett, H. J., Taylor, D. W., Eliasziw, M., Fox, A. J., Ferguson, G. G., Haynes, R. B., et al. (1998). Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med, 339*(20), 1415-25

134. World Health Organization (2001). International Classification of Functioning, Disability and Health: ICF. Geneva, Switzerland: World Health Organization.

135. Tilley, B. C., Marler, J., Geller, N. L., Lu, M., Legler, J., Brott, T., et al. (1996). Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and Stroke t-PA Stroke Trial. *Stroke, 27*(11), 2136-42

136. Ali, M., Fulton, R., Quinn, T., & Brady, M. (2013). How well do standard stroke outcome measures reflect quality of life? A retrospective analysis of clinical trial data. *Stroke, 44*(11), 3161-5

137. Wang, D. Z., Rose, J. A., Honings, D. S., Garwacki, D. J., & Milbrandt, J. C. (2000). Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. *Stroke, 31*(1), 77-81

138. Weimar, C., Ziegler, A., Konig, I. R., & Diener, H. C. (2002). Predicting functional outcome and survival after acute ischemic stroke. *J Neurol, 249*(7), 888-95

139. Johnston, S. C., Wilson, C. B., Halbach, V. V., Higashida, R. T., Dowd, C. F., McDermott, M. W., et al. (2000). Endovascular and surgical treatment of unruptured cerebral aneurysms: comparison of risks. *Ann Neurol, 48*(1), 11-9

140. Bland, J. M., & Altman, D. G. (2002). Statistics Notes: Validating scales and indexes. *Bmj, 324*(7337), 606-7

141. Zhao, H., Collier, J. M., Quah, D. M., Purvis, T., & Bernhardt, J. (2010). The modified Rankin Scale in acute stroke has good inter-rater-reliability but questionable validity. *Cerebrovasc Dis, 29*(2), 188-93

142. New, P. W., & Buchbinder, R. (2006). Critical appraisal and review of the Rankin scale and its derivatives. *Neuroepidemiology, 26*(1), 4-15

143. Torok, M. E., Nguyen, D. B., Tran, T. H., Nguyen, T. B., Thwaites, G. E., Hoang, T. Q., et al. (2011). Dexamethasone and long-term outcome of tuberculous meningitis in Vietnamese adults and adolescents. *PLoS One, 6*(12), e27821

144. Nguyen, T. H., Truong, A. L., Ngo, M. B., Bui, C. T., Dinh, Q. V., Doan, T. C., et al. (2010). Patients with thrombolysed stroke in Vietnam have an excellent outcome: results from the Vietnam Thrombolysis Registry. *Eur J Neurol, 17*(9), 1188-92

145. Lee, K. B., Lim, S. H., Kim, K. H., Kim, K. J., Kim, Y. R., Chang, W. N., et al. (2015). Six-month functional recovery of stroke patients: a multi-time-point study. *Int J Rehabil Res*

146. Jorgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1999). Stroke. Neurologic and functional recovery the Copenhagen Stroke Study. *Phys Med Rehabil Clin N Am, 10*(4), 887-906

147. Jorgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1997). Acute stroke: prognosis and a prediction of the effect of medical treatment on outcome and health care utilization. The Copenhagen Stroke Study. *Neurology, 49*(5), 1335-42

148. Hankey, G. J., Spiesser, J., Hakimi, Z., Bego, G., Carita, P., & Gabriel, S. (2007). Rate, degree, and predictors of recovery from disability following ischemic stroke. *Neurology, 68*(19), 1583-7

149. Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol, 63*(3), 272-87

150. Wade, D. T., Wood, V. A., & Hewer, R. L. (1985). Recovery after stroke--the first 3 months. *J Neurol Neurosurg Psychiatry, 48*(1), 7-13

151. Hallevi, H., Albright, K. C., Martin-Schild, S. B., Barreto, A. D., Morales, M. M., Bornstein, N., et al. (2009). Recovery after ischemic stroke: criteria for good outcome by level of disability at day 7. *Cerebrovasc Dis, 28*(4), 341-8

152. Silvestrelli, G., Parnetti, L., Paciaroni, M., Caso, V., Corea, F., Vitali, R., et al. (2006). Early admission to stroke unit influences clinical outcome. *Eur J Neurol, 13*(3), 250-5

153. Glader, E. L., Stegmayr, B., Norrving, B., Terent, A., Hulter-Asberg, K., Wester, P. O., et al. (2003). Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke, 34*(8), 1970-5

154. Glader, E. L., Stegmayr, B., Johansson, L., Hulter-Asberg, K., & Wester, P. O. (2001). Differences in long-term outcome between patients treated in stroke units and in general wards: a 2-year follow-up of stroke patients in sweden. *Stroke, 32*(9), 2124-30

155. Gattringer, T., Ferrari, J., Knoflach, M., Seyfang, L., Horner, S., Niederkorn, K., et al. (2014). Sex-related differences of acute stroke unit care: results from the Austrian stroke unit registry. *Stroke, 45*(6), 1632-8

156. Liu, G., Ntaios, G., Zheng, H., Wang, Y., Michel, P., Wang, D. Z., et al. (2013). External validation of the ASTRAL score to predict 3- and 12-month functional outcome in the China National Stroke Registry. *Stroke, 44*(5), 1443-5

157. Wang, Y., Cui, L., Ji, X., Dong, Q., Zeng, J., Wang, Y., et al. (2011). The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke, 6*(4), 355-61

158. Kim, C., Jang, M. U., Oh, M. S., Park, J. H., Jung, S., Lee, J. H., et al. (2014). Off-hour effect on 3-month functional outcome after acute ischemic stroke: a prospective multicenter registry. *PLoS One, 9*(8), e105799

159. Heuschmann, P. U., Wiedmann, S., Wellwood, I., Rudd, A., Di Carlo, A., Bejot, Y., et al. (2011). Three-month stroke outcome: the European Registers of Stroke (EROS) investigators. *Neurology, 76*(2), 159-65

160. Di Carlo, A., Lamassa, M., Baldereschi, M., Pracucci, G., Basile, A. M., Wolfe, C. D., et al. (2003). Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. *Stroke, 34*(5), 1114-9

161. Fekete, K., Szatmari, S., Szocs, I., Szekeres, C., Szasz, J., Mihalka, L., et al. (2014). Prestroke alcohol consumption and smoking are not associated with stroke severity, disability at discharge, and case fatality. *J Stroke Cerebrovasc Dis, 23*(1), e31-7

162. Meseguer, E., Labreuche, J., Gonzalez-Valcarcel, J., Sirimarco, G., Guidoux, C., Cabrejo, L., et al. (2014). The smoking paradox: impact of smoking on recanalization in the setting of intra-arterial thrombolysis. *Cerebrovasc Dis Extra, 4*(2), 84-91

163. Kvistad, C. E., Oeygarden, H., Logallo, N., Thomassen, L., Waje-Andreassen, U., & Naess, H. (2014). Is smoking associated with favourable outcome in tPA-treated stroke patients? *Acta Neurol Scand*

164. Rist, P. M., Berger, K., Buring, J. E., Kase, C. S., Gaziano, J. M., & Kurth, T. (2010). Alcohol consumption and functional outcome after stroke in men. *Stroke, 41*(1), 141-6

165. Addo, J., Ayerbe, L., Mohan, K. M., Crichton, S., Sheldenkar, A., Chen, R., et al. (2012). Socioeconomic status and stroke: an updated review. *Stroke, 43*(4), 1186-91

166. Cox, A. M., McKevitt, C., Rudd, A. G., & Wolfe, C. D. A. (2006). Socioeconomic status and stroke. *The Lancet Neurology, 5*(2), 181-88

167. Santalucia, P., Pezzella, F. R., Sessa, M., Monaco, S., Torgano, G., Anticoli, S., et al. (2013). Sex differences in clinical presentation, severity and outcome of stroke: results from a hospital-based registry. *Eur J Intern Med, 24*(2), 167-71

168. Olsen, T. S., Andersen, Z. J., & Andersen, K. K. (2012). Explaining poorer stroke outcomes in women: women surviving 3 months have more severe strokes than men despite a lower 3-month case fatality. *Gend Med, 9*(3), 147-53

169. Krause, D. N., Duckles, S. P., & Pelligrino, D. A. (2006). Influence of sex steroid hormones on cerebrovascular function. *J Appl Physiol (1985), 101*(4), 1252-61

170. Murphy, S. J., McCullough, L. D., & Smith, J. M. (2004). Stroke in the female: role of biological sex and estrogen. *Ilar j, 45*(2), 147-59

171. Liu, F., & McCullough, L. D. (2012). Interactions between age, sex, and hormones in experimental ischemic stroke. *Neurochem Int, 61*(8), 1255-65

172. Dagres, N., Nieuwlaat, R., Vardas, P. E., Andresen, D., Levy, S., Cobbe, S., et al. (2007). Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol, 49*(5), 572-7

173. Wang, T. J., Massaro, J. M., Levy, D., Vasan, R. S., Wolf, P. A., D'Agostino, R. B., et al. (2003). A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *Jama, 290*(8), 1049-56

174. Hart, R. G., Pearce, L. A., McBride, R., Rothbart, R. M., & Asinger, R. W. (1999). Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke, 30*(6), 1223-9

175. Haast, R. A., Gustafson, D. R., & Kiliaan, A. J. (2012). Sex differences in stroke. *J Cereb Blood Flow Metab, 32*(12), 2100-7

176. Bushnell, C., McCullough, L. D., Awad, I. A., Chireau, M. V., Fedder, W. N., Furie, K. L., et al. (2014). Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45*(5), 1545-88

177. Fang, M. C., Singer, D. E., Chang, Y., Hylek, E. M., Henault, L. E., Jensvold, N. G., et al. (2005). Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation, 112*(12), 1687-91

178. Stewart, S., Hart, C. L., Hole, D. J., & McMurray, J. J. (2002). A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med, 113*(5), 359-64

179. Friberg, J., Scharling, H., Gadsboll, N., Truelsen, T., & Jensen, G. B. (2004). Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol, 94*(7), 889-94

180. Azzimondi, G., Bassein, L., Fiorani, L., Nonino, F., Montaguti, U., Celin, D., et al. (1997). Variables associated with hospital arrival time after stroke: effect of delay on the clinical efficiency of early treatment. *Stroke, 28*(3), 537-42

181. Lees, K. R., Bluhmki, E., von Kummer, R., Brott, T. G., Toni, D., Grotta, J. C., et al. (2010). Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet, 375*(9727), 1695-703

182. Kapral, M. K., Degani, N., Hall, R., Fang, J., Saposnik, G., Richards, J., et al. (2011). Gender differences in stroke care and outcomes in Ontario. *Womens Health Issues, 21*(2), 171-6

183. Foerch, C., Misselwitz, B., Humpich, M., Steinmetz, H., Neumann-Haefelin, T., & Sitzer, M. (2007). Sex disparity in the access of elderly patients to acute stroke care. *Stroke, 38*(7), 2123-6

184. Menon, S. C., Pandey, D. K., & Morgenstern, L. B. (1998). Critical factors determining access to acute stroke care. *Neurology, 51*(2), 427-32

185. Cheung, R. T. (2001). Hong Kong patients' knowledge of stroke does not influence time-to-hospital presentation. *J Clin Neurosci, 8*(4), 311-4

186. Barr, J., McKinley, S., O'Brien, E., & Herkes, G. (2006). Patient recognition of and response to symptoms of TIA or stroke. *Neuroepidemiology, 26*(3), 168-75

187. Centers for Disease Control and Prevention (2007). Prehospital and hospital delays after stroke onset--United States, 2005-2006. *MMWR Morb Mortal Wkly Rep, 56*(19), 474-8

188. Nowacki, P., Nowik, M., Bajer-Czajkowska, A., Porebska, A., Zywica, A., Nocon, D., et al. (2007). Patients' and bystanders' awareness of stroke and pre-hospital delay after stroke onset: perspectives for thrombolysis in West Pomerania Province, Poland. *Eur Neurol, 58*(3), 159-65

189. Lacy, C. R., Suh, D. C., Bueno, M., & Kostis, J. B. (2001). Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). *Stroke, 32*(1), 63-9

190. Derex, L., Adeleine, P., Nighoghossian, N., Honnorat, J., & Trouillas, P. (2002). Factors influencing early admission in a French stroke unit. *Stroke, 33*(1), 153-9

191. World Health Organization Quality of Life Group. (1998). The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med, 46*(12), 1569-85

192. World Health Organization Quality of Life Group. (1995). The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med, 41*(10), 1403-9

193. Fayers, P., & Hays, R. (2005). *Assessing quality of life in clinical trials*. New York: Oxford Press.

194. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization (1995). *Soc Sci Med, 41*(10), 1403-9

195. Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care, 30*(6), 473-83

196. Gilson, B. S., Gilson, J. S., Bergner, M., Bobbit, R. A., Kressel, S., Pollard, W. E., et al. (1975). The sickness impact profile. Development of an outcome measure of health care. *Am J Public Health, 65*(12), 1304-10

197. Wiklund, I. (1990). The Nottingham Health Profile--a measure of health-related quality of life. *Scand J Prim Health Care Suppl, 1*, 15-8

198. Parkerson, G. R., Jr., Broadhead, W. E., & Tse, C. K. (1990). The Duke Health Profile. A 17-item measure of health and dysfunction. *Med Care, 28*(11), 1056-72

199. EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy, 16*(3), 199-208

200. Furlong, W. J., Feeny, D. H., Torrance, G. W., & Barr, R. D. (2001). The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. *Ann Med, 33*(5), 375-84

201. Hawthorne, G., Richardson, J., & Osborne, R. (1999). The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res, 8*(3), 209-24

202. Duncan, P. W., Wallace, D., Lai, S. M., Johnson, D., Embretson, S., & Laster, L. J. (1999). The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke, 30*(10), 2131-40

203. Ward, I., Pivko, S., Brooks, G., & Parkin, K. (2011). Validity of the stroke rehabilitation assessment of movement scale in acute rehabilitation: a comparison with the functional independence measure and stroke impact scale-16. *Pm r, 3*(11), 1013-21

204. Hilari, K., Byng, S., Lamping, D. L., & Smith, S. C. (2003). Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39): evaluation of acceptability, reliability, and validity. *Stroke, 34*(8), 1944-50

205. Doyle, P. J., McNeil, M. R., Bost, J. E., Ross, K. B., Wambaugh, J. L., Hula, W. D., et al. (2007). The Burden of Stroke Scale (BOSS) provided valid, reliable, and responsive score estimates of functioning and well-being during the first year of recovery from stroke. *Qual Life Res, 16*(8), 1389-98

206. Mohammad, A. H., Al-Sadat, N., Siew Yim, L., & Chinna, K. (2014). Reliability and validity of the Nigerian (Hausa) version of the Stroke Impact Scale (SIS) 3.0 index. *Biomed Res Int, 2014*, 302097

207. Cael, S., Decavel, P., Binquet, C., Benaim, C., Puyraveau, M., Chotard, M., et al. (2014). Stroke Impact Scale Version 2: Validation of the French Version. *Phys Ther*

208. Goncalves, R. S., Gil, J. N., Cavalheiro, L. M., Costa, R. D., & Ferreira, P. L. (2012). Reliability and validity of the Portuguese version of the Stroke Impact Scale 2.0 (SIS 2.0). *Qual Life Res, 21*(4), 691-6

209. Carod-Artal, F. J., Coral, L. F., Trizotto, D. S., & Moreira, C. M. (2008). The stroke impact scale 3.0: evaluation of acceptability, reliability, and validity of the Brazilian version. *Stroke, 39*(9), 2477-84

210. Kartsona, A., & Hilari, K. (2007). Quality of life in aphasia: Greek adaptation of the stroke and aphasia quality of life scale - 39 item (SAQOL-39). *Eura Medicophys, 43*(1), 27-35

211. Lata-Caneda, M. C., Pineiro-Temprano, M., Garcia-Fraga, I., Garcia-Armesto, I., Barrueco-Egido, J. R., & Meijide-Failde, R. (2009). Spanish adaptation of the Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39). *Eur J Phys Rehabil Med, 45*(3), 379-84

212. Hanh, V. T., Guillemin, F., Cong, D. D., Parkerson, G. R., Jr., Thu, P. B., Quynh, P. T., et al. (2005). Health related quality of life of adolescents in Vietnam: cross-cultural adaptation and validation of the Adolescent Duke Health Profile. *J Adolesc, 28*(1), 127-46

213. Hanh, X. T. V., & Cong, D. D. (2010). Relationship among sociodemographic factors, reported health chronic problems and health-related quality of life: a survey in the adult general population, HCM City, VietNam. *Y Hoc TP. Ho Chi Minh, 14*(2), 218-25

214. Parkerson, G. R., Jr. (2002). *User's guide for Duke Health Measures*.

215. Guillemin, F., Paul-Dauphin, A., Virion, J. M., Bouchet, C., & Briancon, S. (1997). [The DUKE health profile: a generic instrument to measure the quality of life tied to health]. *Sante Publique, 9*(1), 35-44

216. Vo, T. X., Guillemin, F., & Deschamps, J. P. (2005). Psychometric properties of the DUKE Health Profile-adolescent version (DHP-A): a generic instrument for adolescents. *Qual Life Res, 14*(10), 2229-34

217. Briancon, S., Alla, F., Mejat, E., Guillemin, F., Villemot, J. P., Mertes, P. M., et al. (1997). [Measurement of functional inability and quality of life in cardiac failure. Transcultural adaptation and validation of the Goldman, Minnesota and Duke questionnaires]. *Arch Mal Coeur Vaiss, 90*(12), 1577-85

218. Perret-Guillaume, C., Briancon, S., Wahl, D., Guillemin, F., & Empereur, F. (2010). Quality of Life in elderly inpatients with atrial fibrillation as compared with controlled subjects. *J Nutr Health Aging, 14*(2), 161-6

219. Novella, J., Ankri, J., Morrone, I., Guillemin, F., Jolly, D., Jochum, C., et al. (2001). Evaluation of the quality of life in dementia with a generic quality of life questionnaire: the Duke Health Profile. *Dement Geriatr Cogn Disord, 12*(2), 158-66

220. Kranciukaite, D., & Rastenyte, D. (2006). Measurement of quality of life in stroke patients. *Medicina (Kaunas), 42*(9), 709-16

221. Mauldin, P. D., Simpson, K. N., Palesch, Y. Y., Spilker, J. S., Hill, M. D., Khatri, P., et al. (2008). Design of the economic evaluation for the Interventional Management of Stroke (III) trial. *Int J Stroke, 3*(2), 138-44

222. van Exel, N. J., Scholte op Reimer, W. J., & Koopmanschap, M. A. (2004). Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQoL-5D. *Qual Life Res, 13*(2), 427-33

223. Dyer, M. T., Goldsmith, K. A., Sharples, L. S., & Buxton, M. J. (2010). A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes, 8*, 13

224. Schweikert, B., Hahmann, H., & Leidl, R. (2006). Validation of the EuroQol questionnaire in cardiac rehabilitation. *Heart, 92*(1), 62-7

225. Bushnell, D. M., Martin, M. L., Ricci, J. F., & Bracco, A. (2006). Performance of the EQ-5D in patients with irritable bowel syndrome. *Value Health, 9*(2), 90-7

226. Sonntag, M., Konnopka, A., Leichsenring, F., Salzer, S., Beutel, M. E., Herpertz, S., et al. (2013). Reliability, validity and responsiveness of the EQ-5D in assessing and valuing health status in patients with social phobia. *Health Qual Life Outcomes, 11*, 215

227. Carod-Artal, F. J. (2012). Determining quality of life in stroke survivors. *Expert Rev Pharmacoecon Outcomes Res, 12*(2), 199-211

228. Pinto, E. B., Maso, I., Vilela, R. N., Santos, L. C., & Oliveira-Filho, J. (2011). Validation of the EuroQol quality of life questionnaire on stroke victims. *Arq Neuropsiquiatr, 69*(2b), 320-3

229. Hunger, M., Sabariego, C., Stollenwerk, B., Cieza, A., & Leidl, R. (2012). Validity, reliability and responsiveness of the EQ-5D in German stroke patients undergoing rehabilitation. *Qual Life Res, 21*(7), 1205-16

230. Pickard, A. S., Johnson, J. A., Feeny, D. H., Shuaib, A., Carriere, K. C., & Nasser, A. M. (2004). Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke, 35*(2), 607-12

231. Hoi le, V., Chuc, N. T., & Lindholm, L. (2010). Health-related quality of life, and its determinants, among older people in rural Vietnam. *BMC Public Health, 10*, 549

232. Tran, B. X., Ohinmaa, A., Nguyen, L. T., Nguyen, T. A., & Nguyen, T. H. (2011). Determinants of health-related quality of life in adults living with HIV in Vietnam. *AIDS Care, 23*(10), 1236-45

233. Oczkowski, C., & O'Donnell, M. (2010). Reliability of proxy respondents for patients with stroke: a systematic review. *J Stroke Cerebrovasc Dis, 19*(5), 410-6

234. Sneeuw, K. C., Aaronson, N. K., de Haan, R. J., & Limburg, M. (1997). Assessing quality of life after stroke. The value and limitations of proxy ratings. *Stroke, 28*(8), 1541-9

235. Carod-Artal, F. J., Ferreira Coral, L., Stieven Trizotto, D., & Menezes Moreira, C. (2009). Self- and proxy-report agreement on the Stroke Impact Scale. *Stroke, 40*(10), 3308-14

236. Shyu, Y. I., Maa, S. H., Chen, S. T., & Chen, M. C. (2009). Quality of life among older stroke patients in Taiwan during the first year after discharge. *J Clin Nurs, 18*(16), 2320-8

237. Paul, S. L., Sturm, J. W., Dewey, H. M., Donnan, G. A., Macdonell, R. A., & Thrift, A. G. (2005). Long-term outcome in the North East Melbourne Stroke Incidence Study: predictors of quality of life at 5 years after stroke. *Stroke, 36*(10), 2082-6

238. Abdin, E., Subramaniam, M., Vaingankar, J. A., Luo, N., & Chong, S. A. (2014). Population norms for the EQ-5D index scores using Singapore preference weights. *Qual Life Res*

239. Cerniauskaite, M., Quintas, R., Koutsogeorgou, E., Meucci, P., Sattin, D., Leonardi, M., et al. (2012). Quality-of-life and disability in patients with stroke. *Am J Phys Med Rehabil, 91*(13 Suppl 1), S39-47

240. Hackett, M. L., Duncan, J. R., Anderson, C. S., Broad, J. B., & Bonita, R. (2000). Health-related quality of life among long-term survivors of stroke : results from the Auckland Stroke Study, 1991-1992. *Stroke, 31*(2), 440-7

241. Rachpukdee, S., Howteerakul, N., Suwannapong, N., & Tang-Aroonsin, S. (2013). Quality of life of stroke survivors: a 3-month follow-up study. *J Stroke Cerebrovasc Dis, 22*(7), e70-8

242. Owolabi, M. O. (2011). Impact of stroke on health-related quality of life in diverse cultures: the Berlin-Ibadan multicenter international study. *Health Qual Life Outcomes, 9*, 81

243. Rhoda, A. J. (2014). Health related quality of life of patients six months poststroke living in the Western Cape, South Africa. *African Journal of Disability, 3*(1)

244. Robert, A. A., & Zamzami, M. M. (2014). Stroke in Saudi Arabia: a review of the recent literature. *Pan Afr Med J, 17*, 14

245. Gall, S. L., Tran, P. L., Martin, K., Blizzard, L., & Srikanth, V. (2012). Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. *Stroke, 43*(7), 1982-7

246. Alguren, B., Fridlund, B., Cieza, A., Sunnerhagen, K. S., & Christensson, L. (2012). Factors associated with health-related quality of life after stroke: a 1-year prospective cohort study. *Neurorehabil Neural Repair, 26*(3), 266-74

247. Bushnell, C. D., Reeves, M. J., Zhao, X., Pan, W., Prvu-Bettger, J., Zimmer, L., et al. (2014). Sex differences in quality of life after ischemic stroke. *Neurology, 82*(11), 922-31

248. Gurcay, E., Bal, A., & Cakci, A. (2009). Health-related quality of life in first-ever stroke patients. *Ann Saudi Med., 29*(1), 36-40.

249. Abubakar, S. A., & Isezuo, S. A. (2012). Health related quality of life of stroke survivors: experience of a stroke unit. *Int J Biomed Sci, 8*(3), 183-7

250. Nilsson, J., Rana, A. K., Luong, D. H., Winblad, B., & Kabir, Z. N. (2012). Health-related quality of life in old age: a comparison between rural areas in Bangladesh and Vietnam. *Asia Pac J Public Health, 24*(4), 610-9

251. Bottacchi, E., Corso, G., Tosi, P., Morosini, M. V., De Filippis, G., Santoni, L., et al. (2012). The cost of first-ever stroke in Valle d'Aosta, Italy: linking clinical registries and administrative data. *BMC Health Serv Res, 12*, 372

252. Dewey, H. M., Thrift, A. G., Mihalopoulos, C., Carter, R., Macdonell, R. A., McNeil, J. J., et al. (2001). Cost of stroke in Australia from a societal perspective: results from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke, 32*(10), 2409-16

253. Dewey, H. M., Thrift, A. G., Mihalopoulos, C., Carter, R., Macdonell, R. A., McNeil, J. J., et al. (2004). 'Out of pocket' costs to stroke patients during the first year after stroke - results from the North East Melbourne Stroke Incidence Study. *J Clin Neurosci, 11*(2), 134-7

254. Cadilhac, D. A., Carter, R., Thrift, A. G., & Dewey, H. M. (2009). Estimating the long-term costs of ischemic and hemorrhagic stroke for Australia: new evidence derived from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke, 40*(3), 915-21

255. Dewey, H. M., Thrift, A. G., Mihalopoulos, C., Carter, R., Macdonell, R. A., McNeil, J. J., et al. (2002). Informal care for stroke survivors: results from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke, 33*(4), 1028-33

256. Evers, S. M., Struijs, J. N., Ament, A. J., van Genugten, M. L., Jager, J. H., & van den Bos, G. A. (2004). International comparison of stroke cost studies. *Stroke, 35*(5), 1209-15

257. Kaur, P., Kwatra, G., Kaur, R., & Pandian, J. D. (2014). Cost of stroke in low and middle income countries: a systematic review. *Int J Stroke, 9*(6), 678-82

258. Clabaugh, G., & Ward, M. M. (2008). Cost-of-Illness Studies in the United States: A Systematic Review of Methodologies Used for Direct Cost. *Value in Health, 11*(1), 13-21

259. Drummond., M. F., Sculpher., M. J., Torrance., G. W., O'Brien., B. J., & Stoddart., G. L. (2005). *Methods for the Economic Evaluation of Health Care Programmes* (Third ed.). Oxford: Oxford University Press.

260. Luengo-Fernandez, R., Gray, A. M., & Rothwell, P. M. (2009). Costs of stroke using patient-level data: a critical review of the literature. *Stroke, 40*(2), e18-23

261. Birabi, B. N., Oke, K. I., Dienye, P. O., & Okafor, U. C. (2012). Cost burden of post stroke condition in Nigeria: a pilot study. *Glob J Health Sci, 4*(6), 17-22

262. Khealani, B. A., & Wasay, M. (2008). The burden of stroke in Pakistan. *Int J Stroke, 3*(4), 293-6

263. Wei, J. W., Heeley, E. L., Jan, S., Huang, Y., Huang, Q., Wang, J. G., et al. (2010). Variations and determinants of hospital costs for acute stroke in China. *PLoS One, 5*(9)

264. Toure, K., Ndiaye, N. M., Sene Diouf, F., Ndiaye, M., Diallo, A. K., Ndao, A. K., et al. (2005). [Evaluation of the cost of stroke management in Dakar, Senegal]. *Med Trop (Mars), 65*(5), 458-64

265. Musgrove, P., Zeramdini, R., & Carrin, G. (2002). Basic patterns in national health expenditure. *Bull World Health Organ, 80*(2), 134-42

266. Ke, X., Saksena, P., & Holly, A. (2011). The Determinants of Health Expenditure: A Country Level Panel Data Analysis. World Health Organization.

267. Khealani, B. A., Javed, Z. F., Syed, N. A., Shafqat, S., & Wasay, M. (2003). Cost of acute stroke care at a tertiary care hospital in Karachi, Pakistan. *J Pak Med Assoc, 53*(11), 552-5

268. Nor Azlin, M. N., Syed Aljunid, S. J., Noor Azahz, A., Amrizal, M. N., & Saperi, S. (2012). Direct medical cost of stroke: findings from a tertiary hospital in malaysia. *Med J Malaysia, 67*(5), 473-7

269. Kwatra, G., Kaur, P., Toor, G., Badyal, D. K., Kaur, R., Singh, Y., et al. (2013). Cost of stroke from a tertiary center in northwest India. *Neurol India, 61*(6), 627-32

270. Khiaocharoen, O., Pannarunothai, S., & Zungsontiporn, C. (2012). Cost of acute and sub-acute care for stroke patients. *J Med Assoc Thai, 95*(10), 1266-77

271. Christensen, M. C., Valiente, R., Sampaio Silva, G., Lee, W. C., Dutcher, S., Guimaraes Rocha, M. S., et al. (2009). Acute treatment costs of stroke in Brazil. *Neuroepidemiology, 32*(2), 142-9

272. Christensen, M. C., Previgliano, I., Capparelli, F. J., Lerman, D., Lee, W. C., & Wainsztein, N. A. (2009). Acute treatment costs of intracerebral hemorrhage and ischemic stroke in Argentina. *Acta Neurol Scand, 119*(4), 246-53

273. Asil, T., Celik, Y., Sut, N., Celik, A. D., Balci, K., Yilmaz, A., et al. (2011). Cost of acute ischemic and hemorrhagic stroke in Turkey. *Clin Neurol Neurosurg, 113*(2), 111-4

274. Venketasubramanian, N., & Yin, A. (2000). Hospital costs for stroke care in Singapore. *Cerebrovasc Dis, 10*(4), 320-6

275. Chang, H., Yoon, S. S., & Kwon, Y. D. (2013). Categorized hospital charges of acute ischemic stroke according to trial of org 10172 in acute stroke treatment classification. *Neurol India, 61*(6), 633-8

276. Tu, F., Anan, M., Kiyohara, Y., Okada, Y., & Nobutomo, K. (2003). Analysis of hospital charges for ischemic stroke in Fukuoka, Japan. *Health Policy, 66*(3), 239-46

277. Diringer, M. N., Edwards, D. F., Mattson, D. T., Akins, P. T., Sheedy, C. W., Hsu, C. Y., et al. (1999). Predictors of acute hospital costs for treatment of ischemic stroke in an academic center. *Stroke, 30*(4), 724-8

278. Dodel, R. C., Haacke, C., Zamzow, K., Paweilik, S., Spottke, A., Rethfeldt, M., et al. (2004). Resource utilization and costs of stroke unit care in Germany. *Value Health, 7*(2), 144-52

279. Yoon, S. S., Chang, H., & Kwon, Y. D. (2012). Itemized hospital charges for acute cerebral infarction patients influenced by severity in an academic medical center in Korea. *J Clin Neurol, 8*(1), 58-64

280. Chang, K. C., & Tseng, M. C. (2003). Costs of acute care of first-ever ischemic stroke in Taiwan. *Stroke, 34*(11), e219-21

281. Heeley, E., Anderson, C. S., Huang, Y., Jan, S., Li, Y., Liu, M., et al. (2009). Role of health insurance in averting economic hardship in families after acute stroke in China. *Stroke, 40*(6), 2149-56

282. Ministry of Health, V. N. a. W. (2012). Health Service Delivery Profile. http://www.wpro.who.int/health_services/service_delivery_profile_vietnam.pdf. Accessed 30/12 2014.

283. Tran Van Tien, Hoang Thi Phuong, Inke Mathauer, & Nguyen Thi Kim Phuong (2011). A health financing review of Viet Nam with foucus on social health insurance. http://www.who.int/health_financing/documents/oasis_f_11-vietnam.pdf. Accessed 15/04 2014.

284. Tien, T. V., Phuong, H. T., Mathauer, I., & Phuong, N. T. K. (2011). A health financing review of Viet Nam with a focus on social health insurance. *Geneva: World Health Organization*

285. Assembly, T. N. (2008). No. 25/2008/qh12 on law on health insurance. Ha Noi: The National Assembly.

286. Ministry of Health (2013). Joint Annual Health Review 2013. http://jahr.org.vn/downloads/JAHR2013/JAHR2013_Final_EN.pdf.

287. Somanatha, A., Tandon, A., Dao, H. L., Hurt, K. L., & Fuenzalida-Puelma, H. L. (2014). Moving toward universal coverage of social health insurance in Vietnam : assessment and options. *Directions in development ; human development.* . Washington, DC World Bank Group. .

288. Matsushima, M., & Yamada, H. (2013). Public Health Insurance in Vietnam towards Universal Coverage: Identifying the challenges, issues, and problems in its design and organizational practices. Osaka School of International Public Policy, Osaka University.

289. Ministry of Health (1997). Decision 1895/1997/QĐ-BYT on hospital regulations. *CONG BAO*

290. Ministry of Health (2013). Circular 43/2013/TT-BYT on detailing the delineation of areas of professional skills for the system of medical examination and treatment establishments. *CONG BAO*

291. 115 People's Hospital. (2012). Report of 25th anniversary of the hospital. Ho Chi Minh City: 115 People's Hospital.

292. The Government (2003). Decree No.182/2013 on the region-based minimum wage levels applied to laborers. In T. Government (Ed.). Ha Noi.

293. Cong, N. H. (2007). Stroke care in Vietnam. *Int J Stroke*, *2*(4), 279-80

294. National Institute for Health and Care Excellence (2014). Developing a Quality Standard for the Hospital Management of Acute Stroke in Vietnam. http://www.nice.org.uk/About/What-we-do/NICE-International/NICE-International-projects/Quality-Standard-for-the-Hospital-Management-of-Acute-Stroke-in-Vietnam.

295. Gall S, Velandai, S., Magnussen C, Thrift A, Blizzard L, Nguyen TKL, et al. (2010). A hospital-based pilot study assessing stroke admissions and outcomes in Viet Nam. Hobart, Australia: Menzies Research Institute Tasmania.

296. Lee, Y. K., Nam, H. S., Chuang, L. H., Kim, K. Y., Yang, H. K., Kwon, I. S., et al. (2009). South Korean time trade-off values for EQ-5D health states: modeling with observed values for 101 health states. *Value Health, 12*(8), 1187-93

297. Hoang, H. T., Pham, T. L., Vo, T. T., Nguyen, P. K., Doran, C. M., & Hill, P. S. (2008). The costs of traumatic brain injury due to motorcycle accidents in Hanoi, Vietnam. *Cost Eff Resour Alloc, 6*, 17

298. Rosner, B. (2006). *Fundamentals of Biostatistics* (6th ed.). Belmont, CA: Duxbury.

299. Fleiss, J. L., B. Levin, & Paik, M. C. (2003). *Statistical Methods for Rates and Proportions* (3rd ed.). New York: Wiley.

300. Eriksson, M., Glader, E. L., Norrving, B., Terent, A., & Stegmayr, B. (2009). Sex differences in stroke care and outcome in the Swedish national quality register for stroke care. *Stroke, 40*(3), 909-14

301. Palnum, K. D., Andersen, G., Ingeman, A., Krog, B. R., Bartels, P., & Johnsen, S. P. (2009). Sex-related differences in quality of care and short-term mortality among patients with acute stroke in Denmark: a nationwide follow-up study. *Stroke, 40*(4), 1134-9

302. Gargano, J. W., & Reeves, M. J. (2007). Sex differences in stroke recovery and stroke-specific quality of life: results from a statewide stroke registry. *Stroke., 38*(9), 2541-8. Epub 007 Aug 2.

303. Hong, K. S., Kang, D. W., Koo, J. S., Yu, K. H., Han, M. K., Cho, Y. J., et al. (2008). Impact of neurological and medical complications on 3-month outcomes in acute ischaemic stroke. *Eur J Neurol, 15*(12), 1324-31

304. Kim, J. S., Choi-Kwon, S., Kwon, S. U., Lee, H. J., Park, K. A., & Seo, Y. S. (2005). Factors affecting the quality of life after ischemic stroke: young versus old patients. *J Clin Neurol, 1*(1), 59-68

305. Rossnagel, K., Nolte, C. H., Muller-Nordhorn, J., Jungehulsing, G. J., Selim, D., Bruggenjurgen, B., et al. (2005). Medical resource use and costs of health care after acute stroke in Germany. *Eur J Neurol, 12*(11), 862-8

306. Walter, S. D., Eliasziw, M., & Donner, A. (1998). Sample size and optimal designs for reliability studies. *Stat Med, 17*(1), 101-10

307. Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*(1), 159-74

308. World Health Organization (2011). Stroke, Cerebrovascular accident. http://www.who.int/topics/cerebrovascular_accident/en/. Accessed August 15 2011.

309. Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., et al. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions,

1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2197-223

310. McCormack, V. A., & Boffetta, P. (2011). Today's lifestyles, tomorrow's cancers: trends in lifestyle risk factors for cancer in low- and middle-income countries. *Ann Oncol, 22*(11), 2349-57

311. Mackay, J., & Crofton, J. (1996). Tobacco and the developing world. *Br Med Bull, 52*(1), 206-21

312. Blizzard, L., & Hosmer, D. W. (2007). The log multinomial regression model for nominal outcomes with more than two attributes. *Biom J, 49*(6), 889-902

313. Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol, 159*(7), 702-6

314. Ahamad OB, Boschi-Pinto C, Lopez AD, Murray CJL , Lozano R , & Inoue M (2001). Age standardization of rates: a new WHO standard. *GPE Discussion Paper Series: No.31*. Geneva: World Health Organization,.

315. Nguyen, T. T. N., Tran, K. L., Bui, N. L., Vos, T., Ngo, D. A., & Nguyen, T. H. (2011). Vietnam burden of disease and injury study 2008. *The VINE Project 2010-2011*. Hanoi, Vietnam: Ha Noi School of Public Health.

316. David W. Hosmer, J., Stanley Lemeshow, & Rodney X. Sturdivant (2013). *Applied Logistic Regression*. Hoboken, New Jersey: John Wiley and Sons Inc.

317. Blizzard, C., Quinn, S., Canary, J., & Hosmer, D. (2013). Log-Link Regression Models for Ordinal Responses. *Open Journal of Statistics, 3*(4A), 16-25

318. Ovbiagele, B., Liebeskind, D. S., Kim, D., Ali, L. K., Pineda, S., & Saver, J. L. (2011). Prognostic value of Framingham Cardiovascular Risk Score in hospitalized stroke patients. *J Stroke Cerebrovasc Dis, 20*(3), 222-6

319. Wolfe, C. D., Tilling, K., Beech, R., & Rudd, A. G. (1999). Variations in case fatality and dependency from stroke in western and central Europe. The European BIOMED Study of Stroke Care Group. *Stroke, 30*(2), 350-6

320. Wang, J., Ning, X., Yang, L., Tu, J., Gu, H., Zhan, C., et al. (2014). Sex differences in trends of incidence and mortality of first-ever stroke in rural Tianjin, China, from 1992 to 2012. *Stroke, 45*(6), 1626-31

321. Ovbiagele, B., Weir, C. J., Saver, J. L., Muir, K. W., & Lees, K. R. (2006). Effect of smoking status on outcome after acute ischemic stroke. *Cerebrovasc Dis, 21*(4), 260-5

322. Pham, L. T., Blizzard, L., Gall, S. L., Thrift, A. G., Luong, N. K., Truong, L. V. N., et al. (2014). Hospital-based surveillance of stroke over 12 months at a tertiary teaching hospital in Ho Chi Minh City, Viet Nam. Hobart: Menzies Institute for Medical Research.

323. Huybrechts, K. F., & Caro, J. J. (2007). The Barthel Index and modified Rankin Scale as prognostic tools for long-term outcomes after stroke: a qualitative review of the literature. *Curr Med Res Opin, 23*(7), 1627-36

324. Toschke, A. M., Tilling, K., Cox, A. M., Rudd, A. G., Heuschmann, P. U., & Wolfe, C. D. (2010). Patient-specific recovery patterns over time measured by dependence in activities of daily living after stroke and post-stroke care: the South London Stroke Register (SLSR). *Eur J Neurol, 17*(2), 219-25

325. Karatepe, A. G., Gunaydin, R., Kaya, T., & Turkmen, G. (2008). Comorbidity in patients after stroke: impact on functional outcome. *J Rehabil Med, 40*(10), 831-5

326. Grieve, R., Hutton, J., Bhalla, A., Rastenyte, D., Ryglewicz, D., Sarti, C., et al. (2001). A comparison of the costs and survival of hospital-admitted stroke patients across Europe. *Stroke, 32*(7), 1684-91

327. Grieve, R., Dundas, R., Beech, R., & Wolfe, C. (2001). The development and use of a method to compare the costs of acute stroke across Europe. *Age Ageing, 30*(1), 67-72

328. Farrell, B., Godwin, J., Richards, S., & Warlow, C. (1991). The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry, 54*(12), 1044-54

329. DeGraba, T. J., Hallenbeck, J. M., Pettigrew, K. D., Dutka, A. J., & Kelly, B. J. (1999). Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. *Stroke, 30*(6), 1208-12

330. Kanavos, P., & Mossialos, E. (1999). International comparisons of health care expenditures: what we know and what we do not know. *J Health Serv Res Policy, 4*(2), 122-6

331. Blizzard, L., & Hosmer, D. W. (2006). Parameter estimation and goodness-of-fit in log binomial regression. *Biom J, 48*(1), 5-22

332. Greenland, S. (1989). Modeling and variable selection in epidemiologic analysis. *Am J Public Health, 79*(3), 340-9

333. Mamoli, A., Censori, B., Casto, L., Sileo, C., Cesana, B., & Camerlingo, M. (1999). An analysis of the costs of ischemic stroke in an Italian stroke unit. *Neurology, 53*(1), 112-6

334. Pham, L. T., Blizzard, L., Srikanth, V., Thrift, A. G., Nguyen, T. K. L., Nguyen , H. T., et al. (2014). Case-fatality and functional status three months after first-ever stroke in Viet Nam. Hobart: Menzies Institute for Medical Research.

335. Gloede, T. D., Halbach, S. M., Thrift, A. G., Dewey, H. M., Pfaff, H., & Cadilhac, D. A. (2014). Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. *Stroke, 45*(11), 3389-94

336. Tu, F., Tokunaga, S., Deng, Z., & Nobutomo, K. (2002). Analysis of hospital charges for cerebral infarction stroke inpatients in Beijing, People's Republic of China. *Health Policy, 59*(3), 243-56

337. Van Minh, H., Ng, N., Juvekar, S., Razzaque, A., Ashraf, A., Hadi, A., et al. (2008). Self-reported prevalence of chronic diseases and their relation to selected sociodemographic variables: a study in INDEPTH Asian sites, 2005. *Prev Chronic Dis, 5*(3), A86

338. Trinh, O. T., Nguyen, N. D., Phongsavon, P., Dibley, M. J., & Bauman, A. E. (2010). Metabolic risk profiles and associated risk factors among Vietnamese adults in Ho Chi Minh City. *Metab Syndr Relat Disord, 8*(1), 69-78

339. Fitzpatrick, A. L., Ngo, Q. V., Ly, K. A., Ton, T. G., Longstreth, W. T., Jr., Vo, T. T., et al. (2012). Symptoms and risk factors for stroke in a community-based observational sample in Viet Nam. *J Epidemiol Glob Health, 2*(3), 155-63

340. Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological), 57*(1), 289-300

341. Baumann, C., Erpelding, M. L., Perret-Guillaume, C., Gautier, A., Regat, S., Collin, J. F., et al. (2011). Health-related quality of life in French adolescents and adults: norms for the DUKE Health Profile. *BMC Public Health, 11*, 401

342. Cabral, D. L., Laurentino, G. E., Damascena, C. G., Faria, C. D., Melo, P. G., & Teixeira-Salmela, L. F. (2012). Comparisons of the Nottingham Health Profile and the SF-36 health survey for the assessment of quality of life in individuals with chronic stroke. *Rev Bras Fisioter., 16*(4), 301-8. Epub 2012 Jun 21.

343. Samsa, G., Edelman, D., Rothman, M. L., Williams, G. R., Lipscomb, J., & Matchar, D. (1999). Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics, 15*(2), 141-55

344. Norman, G. R., Sloan, J. A., & Wyrwich, K. W. (2003). Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care, 41*(5), 582-92

345. Bouchet, C., Guillemin, F., Paul-Dauphin, A., & Briancon, S. (2000). Selection of quality-of-life measures for a prevention trial: a psychometric analysis. *Control Clin Trials, 21*(1), 30-43

346. Duncan, P. W., Lai, S. M., Tyler, D., Perera, S., Reker, D. M., & Studenski, S. (2002). Evaluation of proxy responses to the Stroke Impact Scale. *Stroke, 33*(11), 2593-9

347. Vellone, E., Savini, S., Simeone, S., Barbato, N., Castrovillano, G., Caramia, M. D., et al. (2011). [Reliability of caregivers in assessing the quality of life of stroke survivors: an explorative study]. *Assist Inferm Ric, 30*(4), 180-8

348. Smith, S. C., Lamping, D. L., Banerjee, S., Harwood, R., Foley, B., Smith, P., et al. (2005). Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess, 9*(10), 1-93, iii-iv

349. Marx, R. G., Menezes, A., Horovitz, L., Jones, E. C., & Warren, R. F. (2003). A comparison of two time intervals for test-retest reliability of health status instruments. *J Clin Epidemiol, 56*(8), 730-5

350. Lindgren, P., Glader, E. L., & Jonsson, B. (2008). Utility loss and indirect costs after stroke in Sweden. *Eur J Cardiovasc Prev Rehabil, 15*(2), 230-3

351. Mayo, N. E., Scott, S. C., Bayley, M., Cheung, A., Garland, J., Jutai, J., et al. (2013). Modeling health-related quality of life in people recovering from stroke. *Qual Life Res*

352. Sprigg, N., Selby, J., Fox, L., Berge, E., Whynes, D., & Bath, P. M. (2013). Very low quality of life after acute stroke: data from the Efficacy of Nitric Oxide in Stroke trial. *Stroke, 44*(12), 3458-62

353. Delcourt, C., Hackett, M., Wu, Y., Huang, Y., Wang, J., Heeley, E., et al. (2011). Determinants of quality of life after stroke in China: the ChinaQUEST (QUality Evaluation of Stroke care and Treatment) study. *Stroke, 42*(2), 433-8

354. Tanwir, S., Montgomery, K., Chari, V., & Nesathurai, S. (2014). Stroke rehabilitation: availability of a family member as caregiver and discharge destination. *Eur J Phys Rehabil Med, 50*(3), 355-62

355. Pereira, S., Foley, N., Salter, K., McClure, J. A., Meyer, M., Brown, J., et al. (2014). Discharge destination of individuals with severe stroke undergoing rehabilitation: a predictive model. *Disabil Rehabil, 36*(9), 727-31

356. Theeke, L., Horstman, P., Mallow, J., Lucke-Wold, N., Culp, S., Domico, J., et al. (2014). Quality of life and loneliness in stroke survivors living in appalachia. *J Neurosci Nurs, 46*(6), E3-e15

357. Hamza, A. M., Al-Sadat, N., Loh, S. Y., & Jahan, N. K. (2014). Predictors of poststroke health-related quality of life in nigerian stroke survivors: a 1-year follow-up study. *Biomed Res Int, 2014*, 350281

358. Rosland, A. M., Heisler, M., Choi, H. J., Silveira, M. J., & Piette, J. D. (2010). Family influences on self-management among functionally independent adults with diabetes or heart failure: do family members hinder as much as they help? *Chronic Illn, 6*(1), 22-33

359. Newbould, J., Taylor, D., & Bury, M. (2006). Lay-led self-management in chronic illness: a review of the evidence. *Chronic Illn, 2*(4), 249-61

360. Lopez-Espuela, F., Zamorano, J. D., Ramirez-Moreno, J. M., Jimenez-Caballero, P. E., Portilla-Cuenca, J. C., Lavado-Garcia, J. M., et al. (2014). Determinants of Quality of Life in Stroke Survivors After 6 Months, from a Comprehensive Stroke Unit: A Longitudinal Study. *Biol Res Nurs*

361. Carod-Artal, F. J., & Egido, J. A. (2009). Quality of life after stroke: the importance of a good recovery. *Cerebrovasc Dis, 27 Suppl 1*, 204-14

362. Kauhanen, M. L., Korpelainen, J. T., Hiltunen, P., Nieminen, P., Sotaniemi, K. A., & Myllyla, V. V. (2000). Domains and determinants of quality of life after stroke caused by brain infarction. *Arch Phys Med Rehabil, 81*(12), 1541-6

363. Persky, R. W., Turtzo, L. C., & McCullough, L. D. (2010). Stroke in women: disparities and outcomes. *Curr Cardiol Rep, 12*(1), 6-13

364. Ahlsio, B., Britton, M., Murray, V., & Theorell, T. (1984). Disablement and quality of life after stroke. *Stroke, 15*(5), 886-90

365. Sekine, M., Chandola, T., Martikainen, P., Marmot, M., & Kagamimori, S. (2010). Sex differences in physical and mental functioning of Japanese civil servants: explanations from work and family characteristics. *Soc Sci Med, 71*(12), 2091-9

366. Cherepanov, D., Palta, M., Fryback, D. G., & Robert, S. A. (2010). Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. *Qual Life Res, 19*(8), 1115-24

367. Carod-Artal, F. J., Casanova Lanchipa, J. O., Cruz Ramírez, L. M., Pérez, N. S., Siacara Aguayo, F. M., Moreno, I. G., et al. (2014). Stroke Subtypes and Comorbidity among Ischemic Stroke Patients in Brasilia and Cuenca: A Brazilian–Spanish Cross-cultural Study. *Journal of Stroke and Cerebrovascular Diseases, 23*(1), 140-47

368. Jorngarden, A., Wettergen, L., & von Essen, L. (2006). Measuring health-related quality of life in adolescents and young adults: Swedish normative data for the SF-36 and the HADS, and the influence of age, gender, and method of administration. *Health Qual Life Outcomes, 4*, 91

369. Mrus, J. M., Williams, P. L., Tsevat, J., Cohn, S. E., & Wu, A. W. (2005). Gender differences in health-related quality of life in patients with HIV/AIDS. *Qual Life Res, 14*(2), 479-91

370. Orfila, F., Ferrer, M., Lamarca, R., Tebe, C., Domingo-Salvany, A., & Alonso, J. (2006). Gender differences in health-related quality of life among the elderly: the role of objective functional capacity and chronic conditions. *Soc Sci Med, 63*(9), 2367-80

371. Sprangers, M. A., de Regt, E. B., Andries, F., van Agt, H. M., Bijl, R. V., de Boer, J. B., et al. (2000). Which chronic conditions are associated with better or poorer quality of life? *J Clin Epidemiol, 53*(9), 895-907

372. Naberan, K., Azpeitia, A., Cantoni, J., & Miravitlles, M. (2012). Impairment of quality of life in women with chronic obstructive pulmonary disease. *Respir Med, 106*(3), 367-73

373. Bourbonnais, J. M., & Samavati, L. (2010). Effect of gender on health related quality of life in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis, 27*(2), 96-102

374. Esteban y Pena, M. M., Hernandez Barrera, V., Fernandez Cordero, X., Gil de Miguel, A., Rodriguez Perez, M., Lopez-de Andres, A., et al. (2010). Self-perception of health status, mental health and quality of life among adults with diabetes residing in a metropolitan area. *Diabetes Metab, 36*(4), 305-11

375. Jansson, K. A., Nemeth, G., Granath, F., Jonsson, B., & Blomqvist, P. (2009). Health-related quality of life (EQ-5D) before and one year after surgery for lumbar spinal stenosis. *J Bone Joint Surg Br, 91*(2), 210-6

376. Appelros, P., Stegmayr, B., & Terent, A. (2010). A review on sex differences in stroke treatment and outcome. *Acta Neurol Scand, 121*(6), 359-69

377. Pham, L. T., Blizzard, L. C., Gall, S. L., Vo, T. X. H., Nguyen, T. K. L., Nguyen , H. T., et al. (2014). Health-related quality of life after stroke: reliability and validity of the Duke Health Profile for use in Viet Nam. Hobart: Menzies Institute for Medical Research.

378. Pickard, A. S., Johnson, J. A., & Feeny, D. H. (2005). Responsiveness of generic health-related quality of life measures in stroke. *Qual Life Res, 14*(1), 207-19

379. Sturm, J. W., Donnan, G. A., Dewey, H. M., Macdonell, R. A., Gilligan, A. K., Srikanth, V., et al. (2004). Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke, 35*(10), 2340-5

380. Jorgensen, H. S., Nakayama, H., Raaschou, H. O., Vive-Larsen, J., Stoier, M., & Olsen, T. S. (1995). Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil, 76*(5), 406-12

381. Gupta, S., Khieu, T. Q., Rao, C., Anh, N., & Hoa, N. P. (2012). Assessing the quality of evidence for verbal autopsy diagnosis of stroke in Vietnam. *J Neurosci Rural Pract, 3*(3), 267-75